

# ABSTRACT E-BOOK

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WORLD CONGRESS ON PARKINSON'S  
DISEASE AND RELATED DISORDERS  
A COMPREHENSIVE EDUCATIONAL PROGRAM

MONTREAL / CANADA

# 2019

16 – 19 June

[www.iaprd-world-congress.com](http://www.iaprd-world-congress.com)



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Abstract Title

Abstract Number

Author name

Source: XXIV World Congress on Parkinson's Disease and Related Disorders  
Montreal, Canada, 16 – 19 June 2019

URN: urn:nbn:de:101:1-2019052912131149587864

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# Videos

## Grand Parade of Movement Disorders

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V003

### Dissociation of resting head and limb tremor - clinicopathological study

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**Objectives:** To determine the pathological basis of dissociated resting head and limb tremor.

**Methods:** A 70 year old man developed upper limb action tremor and speech changes. At age 72 he had scanning speech and mild upper limb action tremor. At age 73 he developed head tremor only when lying down, thus preventing him from going to sleep. He had no head tremor while sitting. Over time he developed mild cerebellar ataxia and parkinsonian features with prominent limb resting and action tremor which coincided with resolution of his head tremor. Evolution of findings was captured on video. Antiparkinsonian drugs produced some improvement of his symptoms however he did not tolerate medications well. He had terminal dysphagia but no nystagmus, gaze palsy, corticospinal or sensory findings. For the final two years he needed nursing home care and died at age 80. Autopsy done within 24 hours of death revealed widespread tau positive neurofibrillary tangles in the brain and spinal cord and significant neuronal loss primarily in the substantia nigra and subthalamic nucleus. Lewy body inclusions were found in the substantia nigra and other nuclei but were restricted to the brainstem.

**Results:** He evolved from upper limb tremor to complicated parkinsonism over 6 years. Brain pathology revealed Parkinson's disease (PD) and progressive supranuclear palsy (PSP).

**Conclusions:** Resting head tremor in this case does not fit the profile of essential tremor and could be due to PD. Although we have documented resolution of limb tremor in PD with time, if the tremor was due to PD we would expect it to follow the same course as the limb tremor. Scanning speech may occur in PSP but resolving resting head tremor is not a known feature.

V004

## A new family with Ataxia-pancytopenia syndrome caused by SAMD9L mutations

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**Objectives:** Mutations in *SAMD9L* gene have recently been associated with the autosomal dominant Ataxia-pancytopenia syndrome, characterized by cerebellar ataxia, variable hematologic cytopenias and predisposition to myelodysplastic syndromes. Here we describe a second family with this rare syndrome from our center.

**Methods:** We compiled the pedigree, examined three family members neurologically and ophthalmologically, and analysed medical records and radiological examinations. A heterozygous germline *SAMD9L* (NM\_152703.4) c.2640C>A, p.(His880Gln) mutation, described in the original paper (Chen PMID: 27259050), was identified by WES and confirmed by Sanger sequencing.

**Results:** Five family members in four generations were affected. All three examined members carried the mutation.

The index patient (video) noted worsening of balance problems at 41 years and had 11 points in the SARA scale at age 50. He had difficulties with gaze fixation and reading, and reduced night vision. Detailed ophthalmological examination revealed paracentral macular dysfunction on multifocal electroretinogram.

His brother had mild balance problems (SARA 3 points) at 46 years, and horizontal nystagmus.

His daughter had myelodysplastic syndrome at age 1,5 years, which reverted spontaneously. She had mild balance problems since teenage years (SARA 1 point) and difficulty reading small print, with subnormal values in multifocal electroretinogram.

Neuroimaging revealed supratentorial white matter changes and marked cerebellar atrophy. Two family members showed prognathia and attached earlobes. One had behavioural problems, and was examined for ADHD, and one had a history of recurrent infections.

**Conclusions:** Patients with Ataxia-pancytopenia syndrome often present with mild gait imbalance, dysarthria or nystagmus, contrasting with a pronounced cerebellar atrophy on imaging. Paracentral retinal dysfunction was also identified in this second family and may be a typical feature of this disease. Also, mild lower facial dysmorphias and ADHD have been described in other families. Regular hematological screening tests in mutation carriers have been recommended due to increased leukemia risk.

## V006

**Three DYT-TUBB4A (DYT4) families with novel mutations**

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DYT-TUBB4A was described in 1985 in a large Australian family. The clinical picture consisted in spasmodic dysphonia and/or cranio-cervical dystonia progressing to generalized dystonia, associated with a peculiar "hobby horse" ataxic gait in some. A heterozygous missense c.4C>G p.R2G mutation in the TUBB4A gene was found and considered pathogenic. Here we report a total of nine patients from three families with three novel TUBB4A variants manifesting isolated dystonia.

Probands were screened by next generation sequencing with a dystonia panel including TUBB4A. All variants found were validated in probands and family members by Sanger sequencing. In silico predictions of pathogenicity were performed using the Combined Annotation-Dependent Depletion (CADD) algorithm. The degree of amino acid conservation among species was assessed through protein multiple sequence alignment using Clustal Omega.

We identified three heterozygous single nucleotide variants in TUBB4A: c.G883A/p.D295N, c.G137T/p.R46M and c.G1272C/Q424H. All variants change highly conserved amino acids and are predicted to be deleterious by in silico analysis (CADD scores 24, 31 and 24.2 respectively). None of them was found in population databases.

The severity of the dystonia ranged from mild to very severe (videos of 7 cases are available). It particularly involved the larynx (7 out of 8 cases) leading to spasmodic dysphonia, the neck (8 out of 9 cases) and the right upper limb (8 out of 8 cases), leading to writer's cramp or more severe arm dystonia. Six of the nine patients had generalized involvement. However, the "hobby horse gait" described in the original Australian family, emphasized by some as characteristic of the disorder, was not found.

TUBB4A mutations lead notably (not only) to isolated dystonia. Spasmodic dysphonia and cervical dystonia are a rather consistent feature (association found in 6 out of 8 cases in the original Australian family ; 7 out of 8 cases in this case series).

V007

## Video case of a patient with congenital mirror movements with features of focal limb dystonia

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**Objectives:** We present a case of a patient who displays focal dystonia in the setting of clinically evident congenital mirror movements.

**Case History:** Patient is a 41yr old RH F with a history of congenital mirror movements. At 3 yrs of age she was first noted to have mirror movements described as a mimicked movement of the uninvolved hand when performing a task. The mirror movements progressed in severity over the year. She recalls sitting on her nondominant hand when writing while in school.

No additional complications up until 2004 when with repetitive activity she developed bilateral carpal tunnel syndrome and had surgical release of the left wrist. She has continued to have left arm pain which progressed to involve the right arm. The pain is associated with dystonic posturing of the right hand and is present with larger movements. She has difficulty writing. She writes in a vertical direction with the page oriented horizontally. No reported family history of congenital mirror movements other than her 2-year old son. She has not had any genetic testing.

**Results:** Congenital mirror movements are a rare disorder with prevalence thought to be less than 1 in 1,000,000. It has autosomal dominant inheritance with gene mutations of DCC or RAD51 gene. This condition may be complicated by dull cramping pain in the extremities with exertion. This is an interesting case of focal dystonia in the setting of congenital mirror movements which may represent common pathophysiology.

**Conclusions:** This video shows apparent mirror movements and unusual posturing while writing representing focal dystonia - writer's cramp.

V008

## Brexpiprazole-induced parkinsonism

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**Objectives:** Brexpiprazole is an atypical antipsychotic medication approved in the US for the treatment of schizophrenia and as an adjunctive treatment of depression. Similar to aripiprazole, brexpiprazole is a partial dopamine agonist, but has less intrinsic activity at the D2 receptor and higher potency at serotonergic and adrenergic receptors. Based on this mechanism of action, it is thought to have a lower risk of extrapyramidal symptoms. While its safety and tolerability profile is favorable, the majority of brexpiprazole clinical trials have focused on younger patients. Here we present a case of brexpiprazole-induced parkinsonism in an elderly woman.

**Methods:** Case report.

**Results:** A 71-year-old woman with a long history of essential tremor involving the hands presented to clinic with new resting tremor in her hands, legs, and jaw. She was found to have asymmetric bradykinesia and rigidity consistent with parkinsonism and started on low dose levodopa. Two months later, she reported drastic worsening of tremor, anterocollis, gait freezing episodes, and a marked decline in mobility. Levodopa was increased to 900 mg per day without improvement. Dopamine transporter scan was normal. It was then discovered that her psychiatrist started brexpiprazole 1 mg daily for severe depression/anxiety around the time of her initial clinic presentation. This was increased to 2 mg daily two months after her initial visit, coinciding with the dramatic worsening of her parkinsonism. One month after stopping brexpiprazole, gait and mobility improved significantly, while rest tremor improved modestly.

**Conclusions:** Brexpiprazole is an antipsychotic medication thought to have lower risk of extrapyramidal symptoms but can cause drug-induced parkinsonism. Most published studies assessing its tolerability have not included elderly patients, so it is possible that this population may be at greater risk.



# Oral Poster Sessions

## Session I - Parkinson's disease: Basic science and genetics

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### OP-01-01

#### **Low prevalence of known pathogenic mutations in dominant PD genes: A Swedish multicenter study**

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**Objectives:** To determine the frequency of mutations known to cause autosomal dominant Parkinson's disease (PD) in a large series with more than 10% of Sweden's estimated number of PD patients.

**Methods:** The Swedish Parkinson's disease Genetics Network was formed as a national multicenter consortium of clinical researchers who collected DNA from Swedish PD patients at their centers. Samples from 2,206 PD patients were analyzed centrally for known pathogenic mutations in *SNCA* (duplications/triplications, p.Ala30Pro, p.Ala53Thr) and *LRRK2* (p.Asn1437His, p.Arg1441His, p.Tyr1699Cys, p.Gly2019Ser, p.Ile2020Thr). We compared the frequency of these mutations in Sweden with previously published PD series, and with data from the gnomAD whole exome database which includes healthy individuals and patients with other disorders.

**Results:** A family history of PD in first- and/or second degree relatives was reported by 21.6% of participants; 85.4% of patients were recruited in population-based studies. Twelve patients (0.54%) carried *LRRK2* p.Gly2019Ser mutations, one patient (0.044%) an *SNCA* duplication. The other mutations tested

were not observed. Previous publications on PD case series generally showed similar mutation frequencies. In gnomAD, LRRK2 p.Gly2019Ser was relatively most common, but only found in 0.049% of 276,858 total alleles, which was largely driven by a 42-fold higher frequency in individuals reporting Ashkenazi Jewish descent. Among 150,438 alleles from European individuals in gnomAD, only 34 carried this mutation (frequency, 0.023%).

**Conclusions:** In relative terms, the LRRK2 p.Gly2019Ser variant is the most frequent mutation among Swedish or international PD patients, and in exome databases. SNCA duplications were the second most common of the mutations examined. In absolute terms, however, these known pathogenic variants in genes causing dominantly-transmitted PD are very rare in Sweden and internationally, and can only explain a minute fraction of the familial aggregation of PD. Additional genetic and environmental mechanisms may explain the frequent co-occurrence of PD in close relatives.

#### OP-01-02

### **Graft-host synaptic connectivity can be chemogenetically inhibited with clinically relevant activators to eliminate graft-induced dyskinesias (GID) without losing anti-parkinsonian benefits of dopaminergic grafts**

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Chemogenetics offer the possibility of reversible circuit specific neuromodulation. JHU37160 is a high affinity water soluble chemogenetic ligand that has safety profile superior to clozapine nitric oxide (CNO), that has been attributed to poor blood brain penetrance and nonspecific effects via production of clozapine. We demonstrate the clinical translational potential of JHU37160 using a cell transplantation paradigm in parkinsonian rats to control GID that has previously required a second stereotactic surgery in graft recipients with Parkinson's disease (PD).

Stable right hemiparkinsonian rats first received left striatal AAV2-Ef1a-mCherry-IRES-WGA-Cre injections followed by stereotactic injections of mouse fetal ventral mesencephalic (FVM) dopaminergic grafts that were transfected with hM4Di, the G-protein mediated inhibitory chemogenetic mediator into the left striatum. Chemogenetic inhibition of graft function and GID was tested using CNO 10mg/kg and JHU37160 for 12wks using behavioral tests and histological confirmation.

All grafted animals showed excellent behavioral recovery from parkinsonism and GID was inducible in all grafts by administering the 6-HT agonist ST-1936 that resemble the clinical phenomenology seen in PD patients that undergo dopaminergic grafting. Vibrissae evoked forelimb placement test (VEFT) showed 56% reduction in right limb usage post-CNO administration ( $p < 0.00001$ ,  $n=8$ ) compared to 71% reduction with JHU37160 administration ( $p < 0.00001$ ,  $n=3$ ). The stepping test (ST) also showed a similar statistically significant effect. Both CNO and JHU37160 were effective in eliminating ST-1936 induced GID, with JHU37160 exhibiting a superior safety profile. Both chemogenetic activators did not cause parkinsonism as measured by VEFT and ST when used in the setting of GID, proving its clinical translational relevance.

This proof of principle experiment shows that stereotactic surgical transplantation of dopaminergic grafts can be made safe and effective by incorporating chemogenetic mediators such as hM4Di and activators such as JHU37160 that allow reversible on-demand neuromodulation in PD

OP-01-03

## The metabotropic glutamate 2 receptor positive allosteric modulator biphenyl-indanone A alleviates psychosis and dyskinesia in the Parkinsonian marmoset

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**Objectives:** We previously demonstrated the effectiveness of metabotropic glutamate 2 (mGlu<sub>2</sub>) receptor activation on L-3,4-dihydroxyphenylalanine (L-DOPA)-induced psychosis-like behaviours (PLBs) and dyskinesia. Here, we seek to determine the effect of the highly selective and brain penetrant mGlu<sub>2</sub> receptor positive allosteric modulator (PAM) biphenyl-indanone A (BINA) in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned marmoset model of Parkinson's disease (PD).

**Methods:** Following MPTP administration to render six common marmosets parkinsonian, animals were injected with L-DOPA/benserazide (L-DOPA) to elicit stable PLBs and dyskinesia. On experimental days, BINA (0.1, 1, 10 mg/kg) or vehicle was administered in combination with L-DOPA, and the severity of PLBs, dyskinesia and parkinsonian disability was assessed.

**Results:** BINA (0.1, 1 and 10 mg/kg) administered in conjunction with L-DOPA, significantly reduced time with disabling PLBs, by  $\approx 64\%$ ,  $\approx 89\%$  and  $\approx 85\%$  (all  $P < 0.001$ ), respectively, when compared to L-DOPA/vehicle. In combination with L-DOPA, BINA (0.1, 1 and 10 mg/kg) also attenuated time with disabling dyskinesia, by  $\approx 77\%$ ,  $\approx 94\%$  and  $\approx 89\%$  (all  $P < 0.001$ ), respectively, compared to L-DOPA/vehicle. The anti-psychotic and anti-dyskinetic effect of BINA was achieved without compromising the therapeutic action of L-DOPA.

**Conclusions:** The mGlu<sub>2</sub> receptor PAM BINA effectively diminished PLBs and dyskinesia in the parkinsonian marmoset model of PD. Taken together with the companion abstracts on mGlu<sub>2</sub> receptor activation with LY-487,379 and LY-354,740, these results provide further support for selective mGlu<sub>2</sub> receptor activation as a promising therapeutic approach to alleviate L-DOPA-related complications in PD.

OP-01-04

## Local field potentials reveal modulations of subthalamic oscillatory activity by promised reward during conflict resolution in Parkinson's disease

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**Objectives:** Cognitive action control depends on cortical-subcortical circuits, involving notably the subthalamic nucleus (STN) which consistently shows an increase in the theta band power during conflict situations. Since cognitive action control in Parkinson's disease (PD) can be influenced by the occurrence of monetary reward, our objective was to investigate whether incentive motivation could modulate STN oscillatory activity during response conflict resolution.

**Methods:** We recorded local field potentials (LFPs) in 30 STN during a motivated Simon task in 16 PD patients who had undergone surgery for deep brain stimulation of the STN.

**Results:** Signal analyses locked on the conflict stimulus onset revealed an increase in the theta band power as usually reported in the literature. However, modulation of theta power by conflict situations was not influenced by the size of the reward cued.

Nevertheless, we identified a significant effect of the reward size on local functional organization in the theta band, which increased with the size of reward during conflict resolution. In addition, after the onset of the reward cue, we observed a stronger decrease in the beta band power for the trials with the highest reward.

**Conclusions:** Our results suggest that the modulation in STN activity reflects how reward stimuli can influence processing during cognitive action control.

OP-01-05

## Ethnicity-specific genome-wide association study in Parkinson's disease

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**Background:** Most genome-wide association study (GWAS) of Parkinson's disease (PD) have been centered on populations of European descent and new PD-susceptibility loci have been limited on non-European populations.

**Objectives:** We aimed to identify new ethnicity-specific genomic variants that are associated with Parkinson's disease (PD).

**Methods:** Study subjects included patients with PD (N=1,070) and healthy controls (N=5,000) who were unrelated and ethnic Koreans. Genomic data was produced by the Korean Chip (K-CHIP), Affymetrix Axiom KORV1.1 (variants number of 827,400), which contains the imputation GWAS grid (505,000 Asian-based grid), functional variants of nonsynonymous exome content (84,000 Korean-based grid and 149,000 cSNPs and InDels selected from 2,000 whole-exome sequencing and 400 whole-genome sequencing data that are polymorphic in Korean), pharmacogenetics variants, variants in genes involved in absorption, distribution, metabolism and excretion (ADME) of drugs, and expression quantitative trait loci (eQTL). Genomic analysis was performed after stringent sample and SNP quality controls.

**Results:** The SNCA SNP rs3796661 had the most significant association with PD (OR=0.69, CI=0.62-0.76,  $P=3.79 \times 10^{-13}$ ). The SLC41A1 SNP rs708726 was the second most significant loci (OR=0.75, CI=0.68-0.83,  $P=1.61 \times 10^{-8}$ ). Other variants in Chromosome 1 and Chromosome 6 showed the significant association with PD after Bonferroni correction.

**Conclusions:** This ethnicity-specific GWAS confirmed the association of the SNCA and PARK16 with PD and suggested other variants in chromosome 6 as new risk loci for PD.

## OP-01-06

**Extremes of survival in Parkinson syndrome**A. Rajput<sup>1</sup>, C. Robinson<sup>2</sup>, M. Farrer<sup>3</sup>, E. Gustavsson<sup>3</sup>, A.H. Rajput<sup>1</sup><sup>1</sup>University of Saskatchewan, Saskatoon, Canada, <sup>2</sup>Saskatchewan Health Authority (Formerly), Saskatoon, Canada, <sup>3</sup>University of British Columbia, Vancouver, Canada

**Objectives:** To identify and compare autopsy-confirmed variants of Parkinson syndrome (PS) with exceptionally long and short survival.

**Methods:** Patients have been followed longitudinally by the same two movement disorder neurologists at Movement Disorders Clinic Saskatchewan (MDCS) since 1968. Patients are given a choice of autopsy at no cost. Autopsy is performed within 24 hours of death. One-half brain is put in -80C freezer and the other half examined by a neuropathologist. The final diagnosis of Parkinson variants was made by the treating neurologist, considering clinical and pathological findings. Genetic studies were performed in the laboratory of Dr. M. Farrer. Autopsied PS patients that survived  $\geq 20$  years from symptom onset were identified; all had onset before age 70. All PS autopsied patients with onset before age 70 but  $< 10$  year survival were then identified.

**Results:** 590 cases have come to autopsy; 445 (75%) had PS. Three hundred sixty (81%) of the PS had Parkinson's disease (PD), 13% progressive supranuclear palsy (PSP) and 6% multiple system atrophy (MSA). Fifty-eight (13%) of all PS had  $\geq 20$  years survival; 49 (85%) of those had PD. A tau pathology subgroup of 5 cases had the longest median (54 years; range 20-61 years) survival.

One had DNAJC12 mutation, one LRRK2 mutation and one had PARK2 (parkin) mutation; the other two cases were sporadic tauopathy. Forty-one PS cases had onset  $< 70$  survived  $< 10$  years.

The most common pathology was PSP 16 (39%) followed by PD 12 (29%), MSA 8 (19.5%) and corticobasal degeneration in 4 (9.8%).

**Conclusions:** PS survival is linked to the underlying pathology. Most cases with  $\geq 20$  years survival (considered "elite") have PD, while PSP is the most common in those with short survival ( $< 10$  years).

## OP-01-07

**Whole-genome DNA methylation and gene expression profiling of peripheral blood in patients with Parkinson's Disease**A. Tafreshi<sup>1</sup>, Z. Chen<sup>2</sup>, Z. Yang<sup>2</sup>, J. Paul<sup>2</sup>, S. Stanbouly<sup>2</sup>, X. Chen<sup>2</sup>, C. Wang<sup>2</sup>, K. Dashtipour<sup>2</sup><sup>1</sup>Keck School of Medicine of University of Southern California, Los Angeles, United States, <sup>2</sup>Loma Linda University School of Medicine, Department of Basic Sciences: Division of Microbiology, Loma Linda, United States

**Objectives:** The goal of this study was to examine the entire DNA methylome and transcriptome of Parkinson's Disease (PD) patients to identify potentially relevant biomarkers and/or genes relevant to disease pathogenesis.

**Methods:** Whole-genome CpG site methylation using reduced-representation bisulfite sequencing and subsequent mRNA sequencing were performed on peripheral blood mononuclear cells of 23 PD patients,

and 21 controls. Differentially methylated genes (DMGs) and differentially expressed genes (DEGs) were annotated. Methylation status of CpG sites flanking transcription start sites (TSSs) was characterized. Pathway enrichment analysis was performed with DAVID Bioinformatics Tool.

**Results:** A total of 2062 and 1798 DMGs were identified for male and female PD patients, respectively, 618 of which overlapped in both males and females. Of these overlapped DMGs, five are genes known to be relevant to the PD disease state: *PRKN*, *ATP8A2*, *GFPT2*, *MAG12*, *SLC12A512*, none of which were differentially expressed in PD patients. A total of 1221 and 1306 DEGs were identified for male and female PD patients, respectively, 453 of which were overlapped in both males and females. Notably, several of these genes belonged to similar functional pathways as the five relevant DMGs (ie. the SLC family, vacuolar ATPase, ATP binding cassette subfamily C). 20 genes that were both DMGs and DEGs in both sexes belonged to a variety of pathways relating to mitochondrial function, tobacco and substance dependence, and dystonia. PD patients also appeared to display a differential pattern of TSS flank methylation.

**Conclusions:** As the first of its kind to sequence the entire DNA methylome in PD patients with subsequent expression analysis, our findings indicate that studies examining only DNA methylation may not successfully identify downstream expression changes and that methylation status flanking TSSs may be a “fingerprint” of PD. We also identified at least 20 novel candidate genes in PD.

## OP-01-08

### The spectrum of mild cognitive impairment in alpha-synucleinopathies

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**Objectives:** To investigate the mild cognitive impairment (MCI) profile in alpha-synucleinopathies including E46K genetic mutation, idiopathic Parkinson's disease (iPD) and dementia with Lewy bodies (DLB).

**Methods:** Seven E46K-carriers (5 symptomatic and 2 asymptomatic), 50 iPD, 8 DLB and 30 healthy controls (HC) underwent a neuropsychological battery assessing five cognitive domains according to the MDS criteria for PD-MCI diagnosis: *Attention- working memory* (Digit Span Backward and Trail Making Test-A); *Executive functions* (Modified-Wisconsin Card Sorting Test and Clock Drawing Test-draw); *Language* (Verbal fluency Test-semantic and MOCA Language Subscale); *Memory* (Hopkins Verbal Learning and Brief Visual Memory Test); *Visuospatial ability* (Clock Drawing Test-copy and Benton Judgment Of Line Orientation). Scores were considered impaired when the score was 1.5 standard deviations (SD) below the mean of the matched HC. MCI was distinguished in single-domain MCI (SDMCI) and multiple-domain MCI (MDMCI). Patients not fulfilling these specific criteria were classified as noMCI.

**Results:** Asymptomatic-E46K was diagnosed as noMCI while 74.5% iPD patients, 80% symptomatic-E46K and 100% DLB patients were diagnosed as MDMCI. Asymptomatic-E46K showed significantly higher scores in executive functions and memory compared with iPD but no significant differences were found compared with HC. Symptomatic-E46K showed significantly lower performance in the five domains when compared with HC and significantly lower performance in executive functions and visuospatial abilities

when compared with iPD. No significant differences were found between symptomatic-E46K and DLB. Moreover, the SD of executive functions ( $SD=-3.96$ ) and visuospatial abilities ( $SD=-6.00$ ) domains were larger in symptomatic-E46K while the SD of language ( $SD=-1.51$ ), attention-working memory ( $SD=-1.79$ ) and memory ( $SD=-3.27$ ) domains were larger in DLB.

**Conclusions:** E46K induces severe cognitive dysfunction. MCI in symptomatic-E46K is more pronounced than in iPD, specifically in executive functions and visuospatial abilities. Similarities between symptomatic-E46K and DLB MCI profile support the existence of more aggressive cognitive phenotype specific for alpha-synucleinopathies.

#### OP-01-09

### Frequency of the mutations in the PARK2, PINK1, DJ1 genes in early-onset Parkinson's disease patients from one neighboring geographical region in Europe

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**Objectives:** Parkinson's disease (PD) is one of the most common neurodegenerative disorders with an important role of genetic factors in the pathogenesis. Mutations in the PARK2, PINK1, DJ1 genes, all of autosomal recessive inheritance, were reported as a cause of early onset forms of PD (EO\_PD) in many populations. The aim of the study is to determine and compare the frequency of PARK2, PINK1 and DJ1 mutations in Polish, German, Ukrainian and Czech EO\_PD patients' cohorts.



**Methods:** A total of 2198 EO\_PD patients (inclusion criterion, age of onset 50 and below) from four neighboring countries were included into this study. All of them were diagnosed with PD by the experienced movement disorders experts. Molecular analysis encompassed identification of rearrangements and point mutations in *PARK2*, *PINK1* and *DJ1*.

**Results:** From the total number of 1661 Polish, 335 German, 141 Ukrainian, 61 Czech PD patients, EO\_PD was diagnosed in 519 (31.2%) Polish, 58 (17.3%) German, 30 (21.3%) Ukrainian, 11 (18.0%) Czech patients. The complete genetic analysis is still in progress, but in the initial data revealed biallelic mutations only in *PARK2* and *PINK1* genes.

**Conclusions:** Data collected so far indicates, that EO\_PD is present in analysed populations. The clinical characteristics of our patients are very similar to previous descriptions of EO\_PD phenotype in other European populations. The molecular analysis results will be presented during the Congress.

#### OP-01-10

### Predictive language comprehension in Parkinson's disease

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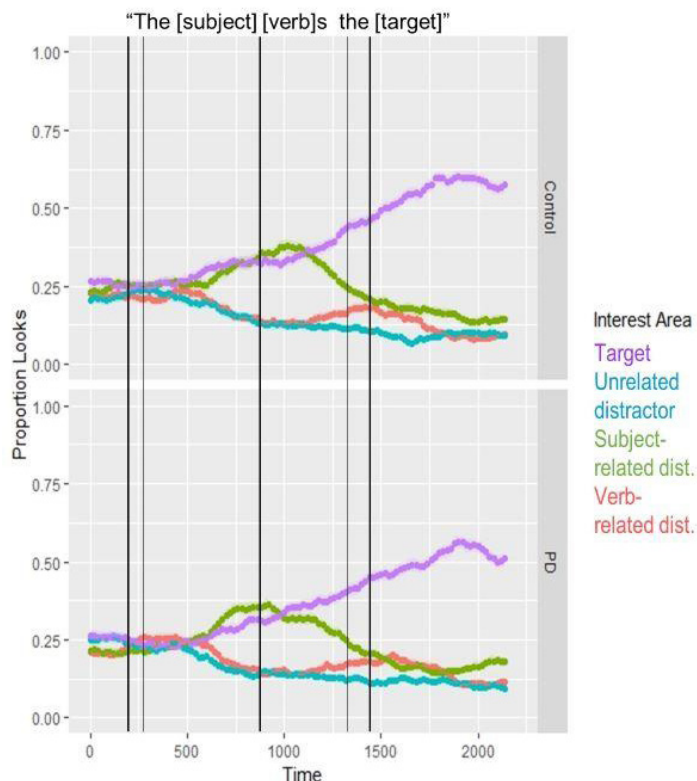
**Objectives:** Individuals process language using probabilistic semantic knowledge developed over a lifetime, according to which subjects/agents and objects/themes are typically associated with specific verbs (e.g., bat-hit-baseball). Consequently, semantic verb deficits in Parkinson's disease (PD) (Bocanegra et al., 2014; Cardona et al., 2013; Roberts et al., 2017) may negatively impact language processing in PD. Yet, few studies have focused on this area. Our objectives are to:

- 1) Test whether individuals with PD are slower or less accurate than healthy controls (HC) in using probabilistic semantic constraints during on-line sentence comprehension.
- 2) Understand how cognitive, language, and disease-related factors predict rapid language comprehension.

**Methods:** Data collection is ongoing. 13 PD and 11 HC participants have completed the eye-tracked visual world paradigm task. In the *prediction* condition, we measure the degree to which participants use implicitly-activated, probabilistic information from a subject+verb to predict the upcoming sentential object (e.g. *The grandmother sews the quilt*). Performance is contrasted with sentences that do not provide strong cues for prediction (e.g. *Look at the boat*). In each condition, we measure the speed and accuracy of anticipatory eye movements to an array of four images (containing 1 target, 1 subject-related distractor, 1 verb-related distractor, and 1 unrelated distractor). Participants also complete a comprehensive neuropsychological battery. A multi-level modeling approach will be used to address the study aims.

**Results:** Preliminary results are presented in Fig. 1. Despite similar PD vs. HC group trends, results suggest substantial individual differences in the integration of semantic information.

**Conclusions:** Preliminary results suggest some individuals with PD show impaired integration of semantic knowledge that may lead to language comprehension difficulties. This finding is important clinically and suggests that some individuals with PD may benefit from existing language therapies that address probabilistic verb knowledge.



[Figure 1: Proportion of looks in predictive sentences in PD vs HC]

#### OP-01-11

### Two-year follow-up bioimpedance change in the body composition of patients with Parkinson's disease

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**Purpose:** To determine the changes in body structure of the Parkinson's disease patients over the last 2 years.

**Material:** The study was conducted 1<sup>st</sup> clinic of the Tashkent Medical Academy in 75 patients (33 female and 42 male) at the age 34-76 years. The test was performed after 2 years, with segmentar body analyzer Tanita BC-545(Japan).

**Results:** Body weight ranged from 52.6 kg to 103 kg, averaging  $69.6 \pm 1.42$  kg. The average body mass index was  $24.8 \pm 0.4$  kg / m<sup>2</sup>, which corresponded to the prevalence among the examined patients with a normal body weight. By the 2nd year of follow-up, patients had BMI decreased by  $1.1 \pm 1.3\%$  ( $p \leq 0.001$ ), from the initial level, where there was a decrease in body weight by 4.6% ( $p \leq 0.01$ ) over the observation period. The decrease in the fat mass content and the proportion of visceral fat was  $2.5 \pm 0.2\%$  ( $p < 0.05$ ) and  $0.1 \pm 0.1\%$ , respectively. The average significant index of lean mass at admission was  $54.0 \pm 1.12$  in patients; at the end of the 2nd year it was  $49.9 \pm 1.1$  ( $p \leq 0.05$ ), which predicted negative weight loss and muscle atrophy due to low level of physical activity. At the same time, patients clinically revealed complaints of fatigue, felt a decrease in strength. The total fat and percentage of fat were significantly higher ( $p < 0.01$ ) and the lean body mass and water content were lower ( $p < 0.001$  for each) in female when compared with males.

**Conclusions:** Was a significant weight loss due to muscle mass during the observation period. It is recommended the appointment of physical therapy, adequate nutrition, care of patients with parkinsonism, effectively helps the normalization of mental, somatic states, affects the motivational component of physical activity with the formation of adequate approaches to a healthy lifestyle.

#### OP-01-12

### Retrospective review on clinical correlations of Parkinson's disease and vascular Parkinsonism in Uzbekistan

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**Objectives:** We aimed to study evidence for or against the role of narrowing lesions of the main brain arteries in progressing of parkinsonism, and to identify clinical signs that suggest a vascular origin.

**Methods:** We provide a Retrospective review in history materials of 231 patients with Parkinson's disease (PD) and Vascular Parkinsonism (VP), 46 and 185 respectively; for the period from 2010 to 2016y. We divided the patients to 2 groups (VP and PD), and compared the clinical features.

**Results:** The both groups were differentiated in terms of evidence of cerebrovascular disease ( $P < .001$  to  $P < .00001$ ). Patients with VP were older, more likely to present with gait difficulty rather than tremor, and less likely to respond to the use of levodopa compared with patients with PD ( $P < .00001$ ). Patients with VP were also significantly more likely to have predominant lower body involvement, postural instability, a history of falling, dementia, corticospinal findings, incontinence ( $P < .00001$ ), and pseudobulbar effect ( $P < .05$ ).

**Conclusions:** These differences in clinical features suggest a different pathogenesis of parkinsonism in these 2 patient groups. The strong evidence of cerebrovascular disease in the VP group and the differences in clinical features support the concept of VP as a distinct clinical entity. We conclude that compared with PD, patients with parkinsonism associated with vascular disease are more likely to present with gait difficulty and postural instability rather than tremor, have a history of stroke and risk factors for stroke, and fail to respond to levodopa therapy.

## Session II - Parkinson's disease: Imaging & Biomarkers/ Other Parkinsonian Disorders

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OP-02-01

### **Optogenetics, functional magnetic resonance imaging, and computational modeling to develop a diagnostic tool for Parkinson's disease**

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**Objectives:** The diagnosis of Parkinson's disease (PD) is based on the observation of clinical symptoms and neurological examinations and significantly relies on the identification of classic motor symptoms. However, the severity of symptoms varies, and misdiagnoses are frequent. There is a critical need to develop a diagnostic tool based on the underlying neurobiology. In response to this, we have designed an interdisciplinary approach.

**Methods:** Our approach combines optogenetics and functional magnetic resonance imaging (fMRI) with a computational method, and uses first animals and then humans. Using optogenetics to switch on a specific type of neuron, and fMRI to map how other regions of the brain respond, we can use computational modeling to generate quantitative descriptions of brain networks with cell-type specificity in animals. Then, we can estimate the contribution of these cell-type-specific networks to the networks estimated with humans.

**Results:** Starting with rodents, we targeted two types of neurons involved in PD. We found that upon stimulation of D1-dopamine neurons, we activated a pathway - the direct pathway - that called for greater motion while when stimulating D2-dopamine neurons, we activated another pathway - the indirect pathway - that called for less motion. We then imaged animals while stimulating either type of neuron and showed how the different neuron types generate distinct whole-brain activation maps. Also, we designed a computational approach to draw circuit diagrams that underlie these neuron-specific brain circuit functions. Now, we aim to use these networks obtained with rodents to estimate the contribution of D1- and D2-neurons to brain-wide activity in healthy subjects and PD patients, and use these contributions as inputs into advanced statistical methods to develop a diagnostic tool.

**Conclusions:** The combination of optogenetics, fMRI, and computational modeling has the potential to lead to significant advancements in the understanding of the biological underpinnings of PD.

## OP-02-02

### Identifying biomarkers for Parkinson's disease with reflex tears

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**Objectives:** To evaluate whether the protein composition of reflex tears differs in individuals with Parkinson's disease (PD) versus Healthy controls (HC)

**Methods:** Reflex tears are stimulated tears collected with an unanesthetized Schirmer's test. Reflex tears were collected from 84 PD patients and 84 age/ sex-matched HC using an unanesthetized Schirmer's test. Samples were pooled from both eyes for analysis of alpha-synuclein, CC chemokine ligand 2 (CCL-2) and total protein. Values were measured by ELISA or multiplex ELISA.

**Results:** Oligomeric alpha-synuclein was significantly increased by 4.7-fold in PD tears ( $4.3 \pm 0.50$  ng/mg tear protein) relative to HC ( $0.89 \pm 0.13$  ng/mg tear protein) ( $p < 0.0001$ , AUC ROC=0.8). CCL2 showed significant increase in PD tears  $165.7 \pm 17.3$  pg/mg tear protein ( $p=0.003$ , AUC ROC=0.63) relative to HC  $122.9 \pm 18.9$  pg/mg tear protein. Average tear secretion is significantly lower in PD patients ( $21.2 \pm 1.8$ mm) compared to HC ( $31.0 \pm 2.2$ mm) ( $p=0.001$ , AUC ROC= 0.65). In male PD patients, changes relative to male HC were noted for oligomeric alpha synuclein ( $5.06 \pm 0.72$  ng/mg tear protein in PD relative to  $0.94 \pm 0.17$  ng/mg tear protein in HC,  $p < 0.0001$ , AUC ROC=0.812) and CCL2 ( $203.8 \pm 27.1$  pg/mg tear protein relative to  $126.5 \pm 30.6$  pg/mg tear protein,  $p=0.0008$ , AUC ROC=0.70), relative to that seen in female PD versus female HC. Diagnostic accuracy as measured by AUC ROC for oligomeric alpha synuclein (0.81) has significantly improved to (0.89,  $p < 0.05$ ) by adding additional markers like CCL2 and Schirmer's value in male PD patients compared to HC.

**Conclusions:** Oligomeric synuclein levels enable discrimination between reflex tears of PD patients and HC. CCL-2 and Schirmer's values may represent additional biomarkers. In males, diagnostic ability can be improved by combining these three biomarkers. The origin of sex differences in biomarker values requires further study.

## OP-02-03

### Impaired topographic organization in drug-naïve Parkinson's disease patients with mild cognitive impairment

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**Background:** Mild cognitive impairment (MCI) is common in Parkinson's disease (PD), and the graph theory approach can be performed to investigate the topographic organization in newly diagnosed drug-naïve PD patients with MCI.

**Methods:** Twenty-two PD patients with MCI (PD-MCI), nineteen PD patients with cognitive unimpaired (PD-CU), and twenty-eight age- and sex-matched healthy controls (HCs) were included. Resting-state functional MRI (fMRI) whole-brain connectivity was examined, and small-world profile and topographic properties were measured, with age, gender and education as covariates. Correlation analyses between topographic features and cognitive scores were performed.

**Results:** Newly diagnosed drug-naïve PD patients and HCs presented the small-world properties, and PD patients had increasing random organizations of brain networks, especially in PD patients with MCI. We also found a descending trend ( $HC > PD-CU > PD-MCI$ ) in the clustering coefficient ( $C_p$ ), characteristic path length ( $L_p$ ) and local efficiency ( $E_{loc}$ ), and a rising trend ( $HC < PD-CU < PD-MCI$ ) in the global efficiency ( $E_{g_{lob}}$ ). Only PD patients with MCI showed decreased nodal centralities in nodes of the sensorimotor network (SMN), default mode network (DMN) and fronto-parietal network (FPN), and increased nodal centralities in nodes of the cingulo-opercular network (CON), FPN and the occipital network. In addition, the increased nodal centralities in the parietal node of the CON negatively correlated with cognitive scores in all PD patients.

**Conclusions:** The study might provide topologic insights into understanding the neural functional changes in relation to the MCI in PD, and contribute to detect the prodromal forms of PD with dementia.

The present study was supported by the fund of National Nature Science Foundation of China (No. 81571247), and the fund of Fundamental Research Funds for the Central Universities (No. 2012017yjsy195).

#### OP-02-04

### Regional cholinergic system correlates of specific cognitive domain changes in Parkinson's disease without dementia

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**Objectives:** Traditionally, the cholinergic system has been viewed as a diffuse neuromodulator system of cognitive functions, but recent studies emphasize a more topographic functional organization. Previous acetylcholinesterase PET imaging studies described attention and executive function correlates of a diffuse loss of cortical cholinergic innervation in PD. Vesicular acetylcholine transporter (VACHT) PET allows for more accurate topographic assessment of cholinergic changes, not only in the cortex but also in the basal ganglia. The purpose of this study was to examine the relationship between cognitive functioning and regional cerebral VACHT binding in PD patients.

**Methods:** A total of 88 PD patients without dementia (77% male, mean (SD) age 67.8 (7.6) years, mean (SD) disease duration of 5.78 (4.63) years) were included in this cross-sectional study. Patients underwent detailed neuropsychological assessment, including memory, attention, executive functions, language and visuospatial abilities. In addition, all subjects underwent VACHT [<sup>18</sup>F]FE0BV brain PET imaging to quantify cholinergic innervation.

**Results:** Global cortical VAcHT binding correlated most robustly with domain scores of memory, attention and execution. Voxel-based whole brain analysis demonstrated specific topographic profiles for each significant cognitive domain, showing the most robust correlations for memory and attention. These domains were especially correlated to the insula, operculum, temporal pole and cingulate cortex. Executive functions showed a strikingly different topographic profile, including the posterior thalamus and lateral geniculate nucleus.

**Conclusions:** The function of the different cognitive domains in PD patients without dementia is correlated to specific cholinergic innervation patterns of the cortex and basal ganglia.

#### OP-02-05

### Effects of free-water correction while comparing diffusion-derived metrics in white-matter skeleton of Parkinson's disease with and without freezing-of-gait

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**Objectives:** To compare diffusion-MRI (dMRI)-derived measures, with and without free-water (FW)-correction, in the white-matter (WM) tracts of Parkinson's disease (PD) patients, with and without freezing-of-gait (FOG); along-with testing their correlation with clinical measures such as Movement Disorder Society sponsored-Unified Parkinson's disease Rating Scale Part-III (MDS-UPDRS-III), Montreal Cognitive Assessment (MoCA), and Mini Mental State Examination (MMSE).

**Methods:** Seventeen PD-FOG patients (13 Males (M) and 4 females (F); Age:  $69.53 \pm 7.01$  years), and twenty-one PD-nFOG patients (14 M and 7F, Age:  $69.05 \pm 6.68$  years) were recruited at our center. 71 directions dMRI dataset was acquired at 3-shells ( $b=500\text{s/mm}^2$ ,  $1000\text{s/mm}^2$ , and  $2500\text{s/mm}^2$ ) with a 3T Siemens Skyra MRI scanner with an isotropic ( $1.5\text{mm}^3$ ) spatial resolution. MMSE, MoCA and MDS-UPDRS-III were administered during the same visit for all participants, under clinically-defined-OFF-condition. FW-correction was performed using all the three dMRI shells. WM skeleton was derived using tract-based-spatial-statistics. Nonparametric statistical comparisons for observing the difference in the means and association with clinical scores were conducted using permutation analysis of linear models. Both FW-corrected and uncorrected dMRI-derived measures were statistically compared. Significance was established at family-wise-error-corrected ( $p_{\text{corr}} < 0.05$ ).

**Results:** Both FW-corrected and FW-uncorrected dMRI measures revealed a negative correlation between MMSE and radial diffusivity (RD), mean diffusivity (MD), and axial diffusivity (AxD) involving superior-longitudinal-fasciculus, corona-radiata, and corpus-callosum in PD-nFOG patients. Only FW-corrected fractional anisotropy (FA) and RD showed a positive correlation with MDS-UPDRS-III in PD-FOG patients. No difference, with and without FW-correction, in any dMRI-derived measures was observed between PD-FOG and PD-nFOG patients.

**Conclusions:** Utilizing a well-characterized high-angular and spatial resolution dMRI dataset of PD-FOG and PD-nFOG patients acquired with multiple-shells, our study revealed that WM dMRI-derived measures may be biased due to FW. Longitudinal analysis of these patients should demonstrate further deterioration of white matter tracts in PD-FOG patients, allowing for more accurate identification of the underlying structures involved.

#### OP-02-06

### Effects of free-water correction while comparing diffusion-derived metrics in white-matter skeleton of Parkinson's disease and healthy controls

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**Objectives:** To compare diffusion-MRI (dMRI)-derived measures, with and without free-water (FW)-correction, in the white-matter (WM) tracts of Parkinson's disease (PD) patients and healthy controls (HC), along with testing their correlation with clinical measures such as Movement Disorder Society sponsored-Unified Parkinson's disease Rating Scale Part-III (MDS-UPDRS-III) and Montreal Cognitive Assessment (MoCA).

**Methods:** Ten PD patients (5 Males (M) and 5 females (F); Age:  $68.4 \pm 7.72$  years), and ten HC (5M and 5F, Age:  $68.4 \pm 2.59$  years) were recruited at our center. 71-directions dMRI dataset was acquired at 3-shells ( $b=500$  s/mm<sup>2</sup>, 1000 s/mm<sup>2</sup>, and 2500 s/mm<sup>2</sup>) with a 3T Siemens Skyra MRI scanner with an isotropic (1.5 mm<sup>3</sup>) spatial resolution. MoCA and MDS-UPDRS-III were administered during the same visit for all participants. The clinical scores were collected under clinically-defined-OFF-condition for PD participants. FW-correction was performed using all the three dMRI-shells. WM skeleton was derived using tract-based-spatial-statistics. Nonparametric statistical comparisons for observing the difference in the means and correlation of dMRI-derived measures with clinical scores were conducted using permutation analysis of linear models. Of note, both FW-corrected and uncorrected dMRI-derived measures were statistically compared. Significance was established at family-wise-error-corrected ( $p_{\text{corr}} < 0.05$ ).

**Results:** FW-uncorrected radial-diffusivity (RD) in HC revealed a negative correlation with MoCA in the right hemisphere, involving superior-longitudinal-fasciculus, corona-radiata, and corpus-callosum. Further, a significant difference in correlation in the same tracts was observed between PD and HC where the slope of RD correlation with MoCA was greater in PD than in HC. Statistical significance was lost after FW-correction. No significant difference in any dMRI-derived measure, with and without FW-correction, was observed between PD and HC.

**Conclusions:** Utilizing a well-characterized high angular and spatial-resolution dMRI dataset of PD and HC acquired with multiple-shells, our study revealed that WM dMRI-derived measures may be biased due to FW, and therefore caution should be exercised when reporting these comparisons in WM skeleton without FW-correction.



## OP-02-07

### Meta-analysis of optical coherence tomography in Parkinson's disease

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**Background:** Parkinson's disease (PD) is a slowly progressive neurologic disease characterized by degeneration of dopaminergic neurons mainly in the substantia nigra. Previous studies have detected retinal nerve layer (RNFL) thickness abnormalities and macular parameters changes using optical coherence tomography (OCT) in PD patients. However, the results have always been inconsistent. Therefore, this meta-analysis is indicated to evaluate RNFL and macular parameters in PD.

**Methods:** A comprehensible search of the literature among the Cochrane Controlled Trials Register, PUBMED and EMBASE was performed, yielding 39 case-control studies eligible for meta-analysis. We included case-control studies that reported data on RNFL thickness and macular volume and thickness in patients with PD and healthy participants. Standardized mean differences were pooled using random-effects models, and heterogeneity was reported as I<sup>2</sup>.

**Results:** The outcome of the study showed that there was a significant difference of average RNFL thickness in PD compared with healthy controls (WMD = -0.59, 95% CI: -0.74 to -0.43,  $P < 0.00001$ ). Also there are significant differences of macular volume (WMD = -0.23, 95% CI: -0.36 to -0.11,  $P = 0.0003$ ) and central foveal thickness (WMD = -4.95, 95% CI: -9.28 to -0.61,  $P = 0.03$ ).

**Conclusions:** There are significant differences in the RNFL thickness, macular volume and central foveal thickness in all quadrants between the two groups. Imaging techniques such as OCT are noninvasive, inexpensive, and fast, and may be useful for neurologic diagnostic biomarkers for early PD patients.

The present study was supported by the fund of National Nature Science Foundation of China (No. 81571247)

## OP-02-08

### Cross-sectional data analysis on plasma levels of vitamin D in Parkinson's disease

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**Objectives:** In recent years, attention has been paid to the role of vitamin D in Parkinson's disease (PD), in fact a greater severity of the disease seems to be associated with a lower serum concentration of this vitamin. This study aims to evaluate the plasma levels of 25(OH) D in PD and to correlate them with cognitive function and nutritional intake of these patients.

**Methods:** Plasma 25(OH) D levels of PD patients recruited from throughout Italy were collected and correlated with anthropometric parameters, Mini Mental State Examination (MMSE) and Food Frequency Questionnaire. Major exclusion criteria were age < 60 yr, vitamin D supplementation.

**Results:** We enrolled 350 PD patients (66.3% male, 33.7% female). Mean age was 70.5 yr (range 61-89) and mean BMI was 26.1 kg/m<sup>2</sup> ( $\pm$  5.4). The mean 25(OH) D level was 17.1 ng/ml ( $\pm$ 8.34) (deficiency). Mean disease duration was 9.9 ( $\pm$  5.7) yr. By simple linear correlation, a significant direct association between 25(OH) D and MMSE score ( $p=0.03$ ) and an inverse association between 25(OH)D and age ( $p< 0.01$ ) was observed. Moreover, an inverse association between 25(OH) D and Hoen and Yahr ( $p=0.01$ ) stage was found. Finally, a direct association between 25(OH)D and intake of vitamin D contained in food ( $p=0.03$ ), PUFA ( $p=0.04$ ), and vitamin B12 ( $p=0.02$ ) was observed.

**Conclusions:** Low 25(OH) D levels correlate with higher age, worse cognitive abilities and worse disease severity. About nutritional data, higher plasma levels of 25(OH)D correlate with consumption of food rich in PUFA and/or vitamin B12 and/or vitamin D. In management of PD patients, dosage of 25(OH) D plasma levels, adequate nutritional intake of vitamin D and vitamin D oral supplementation might be recommended.

**Acknowledgements:** Osservatorio Grana Padano for online food frequency questionnaire; "Brain and Malnutrition in Chronic Diseases Association" and "Fondazione Grigioni per il morbo di Parkinson" for financial support

#### OP-02-10

### Whole-brain mapping of outputs of primary motor cortex in 6-hydroxydopamine-induced hemiparkinsonian rats

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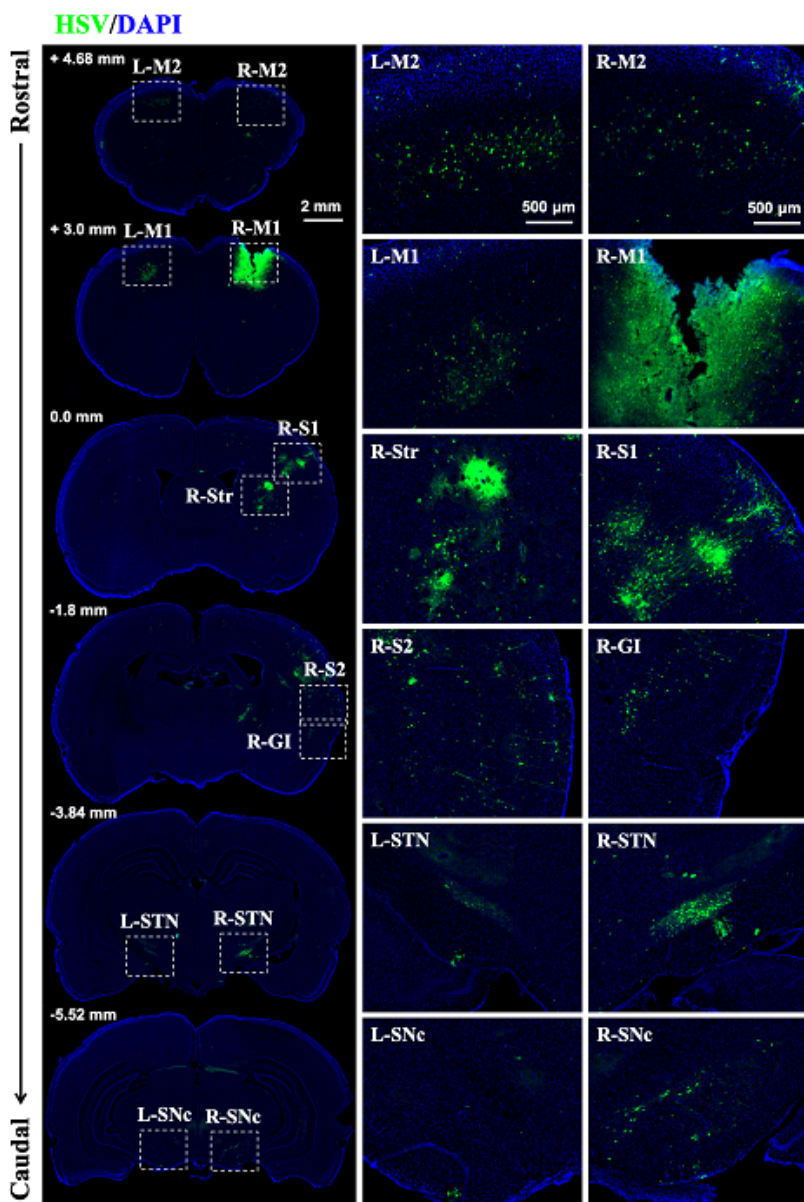
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**Objectives:** Motor cortex-basal ganglia (BG) circuit is the most important circuit for motor modulation. The motor cortex-BG circuit consists of direct, indirect and hyper-direct pathway. In Parkinson's disease (PD), the motor cortex-BG circuit has been shown to be impaired, like the motor cortex-subthalamic nucleus (hyper-direct) connectivity. We wonder if other motor cortex-BG connectivities are also affected in PD. This study aimed to systematically explore the changes of motor cortex-BG connectivities in PD by neural circuitry viral tracing study.

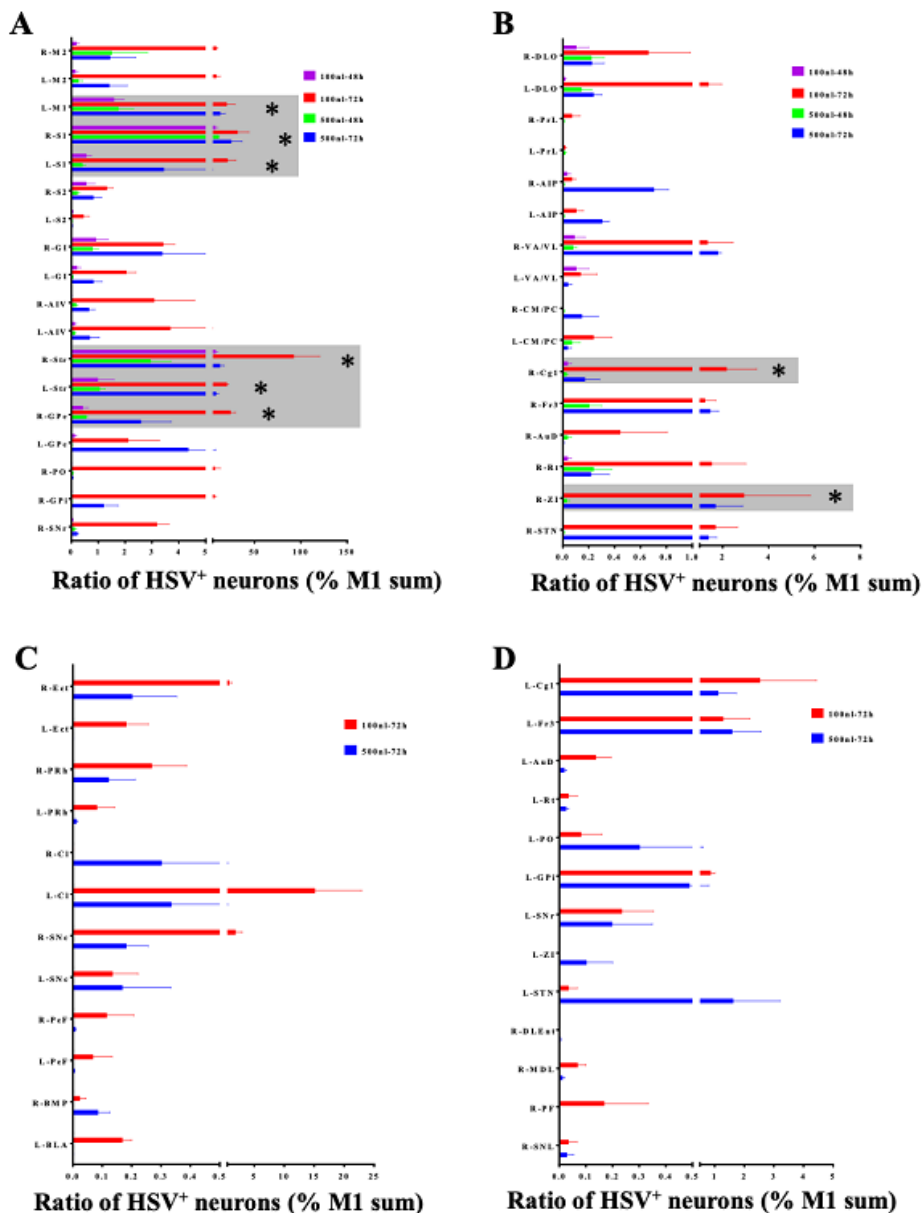
**Methods:** In the present study, we used a trans-synaptic anterograde tracing method with herpes simplex virus-green fluorescent protein (HSV-GFP) to monitor the cortico-BG connectivity in a rat model of PD.

**Results:** We found that neurons of the primary motor cortex (M1) projected to many BG areas, and connectivities from the M1 to many BG areas were impaired in hemiparkinsonian rats as manifested by a marked decreases in trans-synaptic infection of HSV-GFP from M1 neurons to neurons of BG areas like striatum and substantia nigra pars compacta (SNc), in unilateral 6-hydroxydopamine (6-OHDA)-lesioned rats.

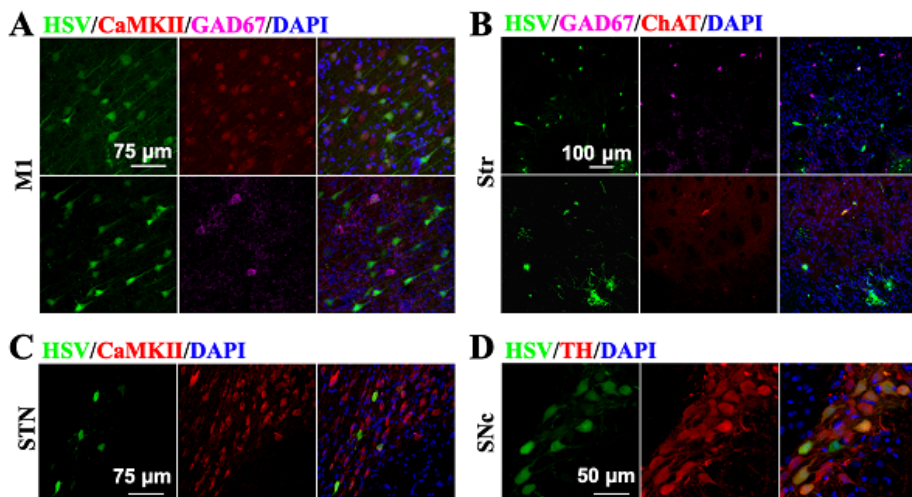
**Conclusions:** We identified whole-brain mapping of outputs of M1 in hemiparkinsonian rats systematically using the HSV-GFP and indicated that many M1-BG connectivities were downregulated in hemiparkinsonian rats.



[Visualization of outputs of M1 using herpes simplex virus-green fluorescent protein (HSV-GFP)]



[Ratio of HSV positive neurons (% M1 sum) in different BG areas at different time]



[The types of HSV positive neurons at different BG areas]

## OP-02-11

### Vascular risk factors and cognition in multiple system atrophy

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**Background:** Vascular risk factors have been reported to be associated with cognitive deficits in the general population, but their role on cognitive impairment in multiple system atrophy (MSA) is unclear. The purpose of the study was to explore the relationship between vascular risk factors and cognition in MSA.

**Methods:** A total of 411 patients with a probable diagnosis of MSA were enrolled. The clinical data of age, sex, height, weight, educational years, disease duration, history of hypertension, diabetes mellitus, smoking, and drinking were collected. Montreal cognitive assessment (MoCA) was used to detect cognitive impairment in MSA. The binary logistic regression was used to analyze the association between vascular risk factors and cognitive impairment.

**Results:** The mean age of onset of MSA patients was  $57.03 \pm 8.68$  years old. Mean disease duration was  $2.48 \pm 1.48$  years. Mean educational years were  $9.76 \pm 3.81$ . In MSA patients, hypertension was recorded in 19.0%, diabetes mellitus 9.0%, current smoker 8.0%, former smoker 34.5%, current drinker 6.8%, former drinker 28.5%, overweight 35.3%, and obesity in 8.3%. one hundred and seventy-six (42.8%) patients had cognitive impairment. In the binary logistic regression model, obesity and present of one vascular risk factor were associated with cognitive impairment in the patients with age of onset  $\leq 57$  years (OR 2.98, 95% CI 1.01-8.79,  $P=0.048$ ; OR 3.09, 95% CI 1.26-7.58,  $P=0.014$ , respectively); obesity was associated with cognitive impairment in MSA-C patients with age of onset  $\leq 57$  years (OR 8.18, 95% CI 1.60-41.92,  $P=0.012$ );

current drinking and former drinking were both associated with cognitive impairment in MSA-P patients with age of onset  $\leq 57$  years (OR 15.33, 95% CI 1.08-217.74,  $P=0.044$ ; OR 5.30, 95% CI 1.24-22.57,  $P=0.024$ , respectively).

**Conclusions:** Vascular risk factors play an important role on cognitive impairment in MSA, especially obesity and drinking, suggesting potential management for vascular risk factors should be considered.

## OP-02-12

### Elevated SNCA expression in CD45+ cells of patients with multiple system atrophy

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**Objectives:** To examine SNCA mRNA levels in CD45+ peripheral blood cells of patients with synucleinopathies: multiple system atrophy (MSA), dementia with Lewy bodies (DLB), Parkinson's disease (PD), Parkinson's disease dementia (PD-D) and individuals without neurological disorders.

**Methods:** For the study we enrolled 183 participants: 11 MSA patients, 84 PD patients, 29 DLB patients and 59 healthy individuals. CD45+ cells were extracted from blood by MACS system (magnetic cell sorting system) (Miltenyi Biotec, USA). SNCA mRNA levels in CD45+ blood cells were estimated by quantitative RT-PCR PCR with iTaq Universal SYBR Green Supermix (Bio-Rad, USA). GNB2L1 mRNA levels were used as internal control. Data calculated using SPSS 24.

**Results:** Median [minimum; maximum] values relative SNCA expression constituted 23,9 (6,4-374,2) for MSA patients, 1,8 (0,18-304,4) for PD-D patients, 0,8 (0,005-12,9) for PD patients, 1,4 (0,08-11,8) for DLB patients and 1,39 (0,01-10,99) for controls. The detected SNCA mRNA levels in patients with MSA were significantly higher as compared to all other groups ( $P < 0,0001$ ). The levels of SNCA mRNA in PD-D patients was higher compare to PD patients ( $P=0,003$ ) and controls ( $P < 0,0001$ ). Interestingly, SNCA mRNA levels in DLB patients were elevated compared to controls ( $P=0,003$ ) but not compared to PD patients ( $P=0,066$ ). There was no difference in the levels of SNCA mRNA between DLB patients and PD-D patients as well as between PD patients and controls.

**Conclusions:** This study is the first to demonstrate dramatic increase in SNCA expression in CD45+ blood cells of MSA patients. Further studies are needed to estimate SNCA mRNA level in CD45+ blood cells as a reliable biomarker of MSA.

This research has been supported by RFBR 18-315-00387 mol\_a grant.

## OP-02-13

### To evaluate the effect of methanolic extract of *Bacopa Monnieri* on scopolamine-induced memory impairment in mice

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**Objectives:** The study was designed in order to evaluate the neuroprotective and anti-amnestic potential of methanolic extract of *Bacopa Monnieri* on scopolamine-induced memory impairment in mice.

**Methods:** Persistent administration of scopolamine (1 mg/kg, *i.p.*) for a period of 7 days remarkably diminished the memory and cognitive performance. Scopolamine has impaired behavioral paradigm (Morris water maze, Y-maze and elevated plus maze) and reduced the antioxidant status (Superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), total thiol proteins and increased the levels of hydroperoxides). Also, it results in increased activity of acetylcholinesterase enzyme, lipid peroxidation and protein carbonyl content in mice model of memory impairment.

**Results:** Two weeks of chronic administration of *Bacopa Monnieri* (30, 60 and 120 mg/kg, *p.o.*) significantly improved cognitive performance (Morris water maze, Y-maze and elevated plus maze) and improved antioxidant status (Superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), total thiol proteins and reduced the level of hydroperoxides) and inhibit acetylcholinesterase enzyme and reduced protein carbonyl level in scopolamine induced memory impairment in mice.

**Conclusions:** *Bacopa Monnieri* possesses strong neuroprotective potential against scopolamine induced memory impairment in mice. The current study reveals the strong potential of *Bacopa Monnieri* in the management of memory impairment.

## OP-02-14

### Autonomic function tests in multiple system atrophy in Vietnam

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**Objectives:** To characterize the pattern and severity of autonomic dysfunction in patients with multiple system atrophy (MSA).

**Methods:** This was a case series study, including 40 patients with MSA. The diagnosis of probable MSA was verified using the second consensus statement on the diagnosis of MSA. In this study, parasympathetic autonomic function was evaluated by the heart rate response to standing (30:15 ratio), heart rate variability with deep breathing, and Valsalva test. Sympathetic autonomic function was evaluated by the sympathetic skin response, blood pressure response to standing, blood pressure response to isometric exercise (sustained handgrip), and cold pressor test.

**Results:** Among 40 subjects (mean (SD), age at diagnosis, 59.4 (7.5) years, Unified MSA Rating Scale score, 31.5 (15)), 29 cases were diagnosed as having MSA-C and 11 as having MSA-P. Thirty six (90%) of the MSA patients showed dysfunction of both sympathetic and parasympathetic systems. Orthostatic hypotension was detected in 28 patients (70%). Sympathetic skin responses were absent in 57.5%. Heart rate response

to standing, heart rate variability with deep breathing, heart rate response to Valsalva test, blood pressure response to isometric exercise, and cold pressor test were abnormal in 50%, 85%, 70%, 70%, and 60%, respectively. The highest frequency of abnormality was observed in R-R variation during deep breathing test (average heart rate variation (SD), 5.1 (3.2) beats/min).

**Conclusions:** The results of this study showed severe abnormalities of both sympathetic and parasympathetic functions in MSA patients. Abnormal autonomic function tests were found in the range of 50% - 85%. Heart rate variability with deep breathing test was the most frequent abnormality.



## Session III - Parkinson's disease: Clinical science, therapeutics, surgical management

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### OP-03-01

### Real world droxidopa and midodrine treatment persistence in patients with orthostatic hypotension

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**Objectives:** To determine the real world treatment persistence of droxidopa and midodrine in patients with neurogenic orthostatic hypotension (nOH) or orthostatic hypotension (OH)

**Background:** OH is a sustained drop in blood pressure upon standing that can lead to falls, impaired function, and poor quality of life; nOH is OH with a neurogenic etiology. Droxidopa and midodrine are approved in the United States to treat symptomatic nOH and symptomatic OH, respectively.

**Methods:** Retrospective analyses of patients prescribed either droxidopa or midodrine were performed using the Symphony Health Solutions Database (Symphony Health; Conshohocken, PA, USA). Inclusion criteria were continuous healthcare utilization from mid-2014 to 2018 and an active prescription for droxidopa or midodrine of  $\geq 30$  days' duration during that period. Persistence was capped at 365 days. Statistical difference between estimated Kaplan-Meier survival curves for droxidopa and midodrine was calculated using a log-rank test and a multivariable Cox regression analysis. Multi-variable hazard ratios were calculated using a Cox proportional hazards model.

**Results:** Data from 2305 patients who received droxidopa (54.2%  $\geq 65$  years of age; 52.9% women) and 117,243 patients who received midodrine (46.7%  $\geq 65$  years of age; 57.6% women) were included. Patient diagnoses in the droxidopa and midodrine groups included Parkinson's disease (30.1% and 6.0%, respectively) and cardiovascular disease (58.6% and 61.6%, respectively). Of the patients with Parkinson's disease, 19.2% and 4.3% in the droxidopa and midodrine groups (respectively) had comorbid cardiovascular disease. Median (95% CI) persistence was significantly longer in the droxidopa cohort vs the midodrine cohort (303 [274-325] vs 172 [169-176] days;  $P < 0.0001$ ). After adjustment for confounding factors, patients on droxidopa were 33% more likely to be persistent (remain on their medication) than patients on midodrine ( $P < 0.0001$ ).

**Conclusions:** In this real-world data analysis, patients using droxidopa were more likely to remain on treatment than patients on midodrine.

## OP-03-02

**Cognitive impairment in Japanese RBD Patients: From the data of J-PPMI study**

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**Objectives:** Idiopathic Rapid eye movement (REM) sleep behavior disorder (RBD) is a symptom specific to prodromal Parkinson's Disease (PD) and attracts attention as a disease that develops a neurodegenerative disease at a high rate. In order to search for prodromal biomarkers for synucleinopathies and discover the disease modified therapy, this prospective cohort study (J-PPMI; The Japan Parkinson's Progression Markers Initiative) was started for patients with RBD.

**Methods:** We launched J-PPMI study at five facilities in Japan. This study comprised 109 individuals with video-polysomnography-confirmed RBD who underwent clinical, imaging and biospecimen biomarker assessment longitudinally for 8 years at five clinical sites, using standardized data acquisition protocols. In the present report, we focused on analyzing data from the baseline assessment, especially cognitive impairments.

**Results:** We show the results of the initial evaluation of J-PPMI in 109 patients which were enrolled in the study. These results can be said to be cross-sectional survey results of RBD patients in Japan. They had mild cognitive dysfunction and olfactory impairment. The heart-to-mediastinum (H/M) ratios for delay images in MIBG myocardial scintigraphy was remarkably low. More than 50% of the patients showed low putaminal specific binding ratio (SBR) in dopamine transporter (DAT) SPECT imaging. The reduced SBR group had poorly performance on cognitive test measuring attention, executive function, delayed recall and orientation compared to the normal SBR group.

**Conclusions:** Prior to the appearance of PD motor symptoms, almost all cases of RBD showed a decrease in cardiac accumulation of MIBG myocardial scintigraphy, and in about half, the reduction of accumulation of striatum by DAT-SPECT was observed. Patients with RBD show also mild cognitive decline and their impaired domain resembles cognitive dysfunction of PD. RBD is already considered to be the precursor stage of  $\alpha$ -synucleinopathy.

OP-03-03

## Long-term progression and prognosis in different subtypes of Parkinson's disease: Validation of a new multi-domain subtyping method

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**Objectives:** Parkinson's disease (PD) varies in clinical manifestations and course of progression from person to person. Identification of distinct PD subtypes is of great priority to develop personalized care approaches. We aim to compare long-term progression and prognosis between different PD subtypes using a new multi-domain subtyping method based on initial motor and non-motor manifestations at the drug-naïve early stage.

**Methods:** Data on 421 individuals with *de novo* early-onset PD (average PD duration: 6.5±6.5 months) was retrieved from Parkinson's Progression Markers Initiative (PPMI). Using a newly developed multi-domain subtyping method (based on motor phenotype, REM sleep behavior disorder (RBD), autonomic disturbance, and early cognitive deficit), we divided PD population into three subtypes at baseline: "*mild motor-predominant*", "*Diffuse malignant*" and "*Intermediate*". Rate of global progression (mixed motor and non-motor features), Schwab and England activities of daily living (SE-ADL) and developing dementia were compared between the subtypes. At the time of data retrieval (January 2019), the median follow-up time was 6 (range:1-8) yrs.

**Results:** Patients with "*diffuse malignant*" PD at baseline, experienced 0.5 z-score further worsening of global composite outcome ( $p=0.017$ ), 2.2 further decline in MOCA score ( $p=0.001$ ) and 5.3% further decline in SE-ADL ( $p=0.010$ ) after 6-years of follow-up. Hazard for MCI/dementia was significantly higher in "*diffuse malignant*" (HR=3.2,  $p<0.001$ ) and "*intermediate*" (HR=1.8,  $p<0.001$ ) subtypes compared to those subtyped as "*mild motor-predominant*". Individuals with "*diffuse malignant*" PD had the lowest level of CSF amyloid-beta ( $p=0.006$ ) and SPECT striatal binding ratio ( $p=0.001$ ).

**Conclusions:** This innovative multi-domain subtyping, which is based on initial motor phenotype and three key non-motor features, is a valid method to predict subgroups of PD with distinct pattern of long-term progression. This subtyping can now be applied to individual patients in real-life clinical practice, at drug-naïve early-stage, using baseline motor and non-motor information to predict course of PD progression.

OP-03-04

## Safety and tolerability of apomorphine sublingual film during maintenance treatment in patients with Parkinson's disease and "OFF" episodes: A pooled analysis

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**Objectives:** To examine safety and tolerability of apomorphine sublingual film (APL-130277; APL) during maintenance treatment using pooled data from 4 clinical studies in patients with Parkinson's disease (PD) and "OFF" episodes.

**Methods:** Adult levodopa-responsive patients with PD and "OFF" episodes exposed to  $\geq 1$  dose of APL (10-60 mg/dose) were included. Treatment-emergent adverse events (TEAEs) were reported using descriptive statistics. Time to onset of TEAEs was assessed using Kaplan-Meier analysis.

**Results:** Among the 285 unique patients in the pooled maintenance treatment phase, median exposure was 85 days (range, 1-283 days) and half received APL for 3 to < 9 months. Overall, 75% of patients reported  $\geq 1$  TEAE; the most common ( $\geq 5\%$ ) were nausea (17%), somnolence (7%), dizziness (6%), fall, fatigue, lip swelling, oral mucosal erythema, vomiting, and yawning (5% each). As a category of special interest, oropharyngeal TEAEs were the most common occurring in 29% of patients. Overall, TEAEs led to APL discontinuation in 25% of patients with oropharyngeal TEAEs being the most common reason for discontinuation. Incidence of TEAEs was similar among patients receiving APL doses < 35 mg (75%) and  $\geq 35$  mg (73%); the lowest incidence reported was with the 10-mg dose (63%), with no trends observed across higher doses. Time to first TEAE was < 1 week for 32% of patients,  $\geq 1$ -12 weeks for 54% of patients, >12-24 weeks for 22% of patients, and >24 weeks for 7% of patients. The only TEAE with an onset < 1 week and reported by  $\geq 5\%$  of patients was nausea (9%).

**Conclusions:** During the pooled maintenance treatment phase, APL was well tolerated and observed TEAEs were generally mild to moderate. Safety findings were consistent with known effects of apomorphine and dopamine agonists except for local site reactions associated with sublingual administration.

**Development of equations to support simulation of progression of motor and non-motor symptoms: Retrospective analysis of the Parkinson's Progression Markers Initiative (PPMI) cohort**

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**Objectives:** To develop equations describing the longitudinal changes after diagnosis of three subscale scores of the Movement Disorder Society sponsored Unified Parkinson's Disease Rating Scale [MDS-UPDRS Parts 1,2, and 3] suitable for use in a simulation of Parkinson's disease progression that can be leveraged to support the development of new disease-modifying treatments.

**Methods:** Longitudinal data were obtained from the Parkinson's Progression Markers Initiative (PPMI) study ([www.ppmi-info.org/data](http://www.ppmi-info.org/data), accessed January 2018, N=423, mean age 61.7 years, disease duration 6.6 years at baseline followed for up to 6.8 years). The data were analysed using Mixed-effect Model Repeated Measures (MMRM) to predict change from previous values of MDS-UPDRS Part 1 (non-motor experiences of daily living), 2 (motor experiences), and 3 (motor examinations).The approach aimed to identify impact of predictors of change in subscale scores and also capture the dependence between these subscales, leveraging prior values and rates of change of the subscale.

**Results:** Predictors assessed included sociodemographics, glucocerebrosidase gene mutation, alpha-synuclein, medical history, medications and disease severity measures. Significant predictors for each subscale are presented in Table 1. These equations performed well in validation analyses.

**Conclusions:** The derived equations capture both established predictors of disease progression such as age, disease duration, and gender, and the association between MDS-UPDRS subscales for non-motor and motor symptoms.

Predictors	MDS-UPDRS-1	MDS-UPDRS-2	MDS-UPDRS-3
Age	Y	Y	Y
Gender	-	Y	Y
Disease duration	Y	-	Y
Alpha-synuclein	Y	-	-
Dopaminergic medication use	-	Y	Y
Baseline MDS-UPDRS	Y Part 2	-	Y Part 3
Prior MDS-UPDRS	Y Part 1, Part 2	Y Part 1, Part 2	Y Part 1, Part 2, Part 3
Time from prior score	Y	Y	Y

[Table 1 : Predictors of MDS-UPDRS 1, 2 or 3 subscales (Y=Significant predictor)]

## OP-03-06

**Effects of regular use of  $\beta$ 2-Adrenergic receptor agonists on the risk of Parkinson's disease in patients with COPD**M. Etmann<sup>1</sup>, A. Samii<sup>2</sup>, H. Tavakoli<sup>1</sup>, C. Wenjia<sup>1</sup>, M. Sadatsafavi<sup>1</sup><sup>1</sup>University of British Columbia, Vancouver, Canada, <sup>2</sup>University of Washington, Seattle, Canada

**Objectives:** Patients with chronic obstructive pulmonary disease (COPD) have shown to have an elevated risk of Parkinson's disease (PD) whereas  $\beta$ 2-adrenoreceptor agonists are associated with lower risk of PD. It remains unclear whether and how  $\beta$ 2-agonist use affects the risk of PD in COPD patients. To examine this association we undertook a large population based pharmacoepidemiologic study.

**Methods:** We performed a nested case-control study based on the health administrative data of British Columbia, Canada (1997-2015). Individuals with  $\geq 40$  years of age were included if they satisfied a validated case definition of COPD. Within the COPD cohort, we identified a PD sub-cohort in which patients have incurred  $\geq 1$  PD-related healthcare encounter and then filled  $\geq 1$  anti-PD medication within 90 days after the initial PD diagnosis, with the initial anti-PD dispensation marked the index date.

Each PD patient was then matched to five COPD patients without PD.  $\beta$ 2-agonist use was measured every six months within the first two years of COPD diagnosis categorized into regular use ( $\geq 1$  dispensation for every six months), irregular use (no dispensation in 1-3 six-month periods) and no use (no dispensation at all).

Conditional logistic regression was used to control for age, socioeconomic status, rurality, comorbidity, any neurologist visit and calendar year as measured at index year.

**Results:** From 242,641 COPD patients, the final analysis included 662 patients in the PD sub-cohort and 3310 in the non-PD sub-cohorts (a 1:5 ratio). Therapeutic use of  $\beta$ 2-agonists did not significantly affect the subsequent two-year risk of PD (*versus no use*, hazard ratios: *regular use*, 0.93 [95% CI: 0.76-1.16,  $p=0.53$ ], *irregular use*, 0.96 [95% CI: 0.75-1.22,  $p=0.72$ ]).

**Conclusions:** In a population-based sample of surviving COPD patients, this rigorous nested case-control study shows that  $\beta$ 2-agonists users have a similar risk of developing PD as compared to the non-users.

## OP-03-07

**The effect of seasonal change on neurogenic orthostatic hypotension in Parkinson's disease**S. Barbu<sup>1</sup>, A. Lieberman<sup>1</sup>, N. Salins<sup>1</sup>, S. Oravivattanakul<sup>1</sup>, G. Moguel-Cobos<sup>1</sup>, R. Walsh<sup>1</sup>, H.A. Shill<sup>1</sup><sup>1</sup>Barrow Neurological Institute, Phoenix, United States

**Objectives:** Neurogenic orthostatic hypotension (NOH) has frequently been seen in Parkinson's disease (PD) but there are few studies on the effect of seasonal change on NOH severity. We conducted a retrospective chart review examining the degree of orthostatic blood pressure (BP) change in PD patients from winter to summer months and vice versa.

Secondary objectives examined the association between NOH and age, gender, PD duration, PD medications, comorbidities, and medications for comorbidities.

**Methods:** A retrospective study analyzing the clinical data of a cohort of 811 PD patients with visits from January 2014 to August 2018. Clinical measures involved orthostatic BP measurements. The study excluded 261 patients without consecutive orthostatic vital signs or who lacked PD diagnosis.

Final analysis was done on 550 patients who had consecutive office visits in the summer and winter months.

**Results:** Out of 550 patients, 22.4% were diagnosed with NOH and 21.8% more met criteria for NOH but were not diagnosed as such. There was no significant change in degree of orthostatic systolic and diastolic BP measurements from summer to winter months in NOH patients (systolic BP  $p=0.561$ ; diastolic BP  $p=0.617$ ) and vice versa (systolic BP  $p=0.571$ ; diastolic BP  $p=0.667$ ).

Analysis of secondary endpoints revealed an association between NOH and age  $\geq 65$  (OR=1.7, 95% confidence interval (CI) 1.1 to 2.6,  $p=0.011$ ), months of PD  $\geq 96$  (OR=1.6, 95% CI 1.1 to 2.2,  $p=0.009$ ), and  $\geq 2$  comorbidities (OR=2, 95% CI 1.1 to 3.5,  $p=0.014$ ). There was no significant association between NOH and gender, hypertensive medications, number of PD medications, Levodopa equivalents, or number of medications for comorbidities.

**Conclusions:** This study showed no significant difference in the degree of NOH between summer and winter months which argues against warm climates exacerbating NOH.

#### OP-03-08

### Exploring the new frontier of synergy and coupling of music with dance movement to modify the course of Parkinson's disease (PD): Synthesis of evidence

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**Introduction:** Despite recent advances in pharmacotherapy, gait imbalance and freezing, accompanied with visual-spatial deficits, confers significant disease burden in terms of interfering with independence living and impaired quality of life. Growing evidence suggests that music-based dance movement therapy may improve motor and non-motor symptoms

**Objective:** The objective of our study is threefold: 1) to search for PubMed reviews and meta-analysis to determine the strength of evidence for specific recommendations for music-guided dance movement therapy in PD; 2) to understand how neuroimaging studies may delineate the neurobiological basis for possible effects of music-coupled-dance movement (MCD) in shifting PD phenotype; 3) to identify the barriers and facilitators in developing outcome-driven community-based MCD.

**Results:** We found three systematic reviews on the MCD for the past 10 years. However, we were unable to conduct meta-regression analysis due to the highly heterogeneity of the dance movement practices in the randomized or non-randomized controlled studies and consensus statements. Standardized PD severity: Unified-Parkinson's-Disease-Rating-Scale (UPDRS) Motor subscale 3 has not been consistently used. The "on" and "off" phases of PD as influenced by the PD drug regimen are often not defined.

While Tango dance is the favorite dance movement, American ballroom dance, Sardinian dance, Salsa dance have not been vigorously examined, The rhythmic auditory stimulation is often coupled with dance movement, while music-derived emotional and behavioral repertoire is not defined.

**Conclusion:** We conclude that two 1-hour dance classes per week over 10-13 weeks may have beneficial sustained effects on muscle endurance, motor impairment, and gait balance. Neuroimaging studies provides exciting evidence for cross talks of: limbic cortex (hippocampus, amygdala, nucleus accumbens) regulating reward and drive, the motor cortex and the basal ganglia. Empowerment and instilling hope to PD, harnessing community resources, can drive culture-sensitive fiscal-responsible integration of MCD into mainstream PD therapeutics to enhance quality-of-life outcome.

#### OP-03-09

### Outcomes of a prospective, multicenter, international registry of deep brain stimulation for Parkinson's disease

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**Objectives:** The effectiveness of Deep Brain Stimulation (DBS) for reducing motor complications of Parkinson's disease (PD) has been substantiated by randomized controlled trials (Schuepbach et al., 2013). Additionally, motor improvement is sustained for up to 10 years (Deuschl et al. 2013). Large patient data registries may facilitate insights regarding real world, clinical use of DBS. Furthermore, no registry database currently exists for a multiple-source, constant current DBS system. Here we describe collected outcomes from a large-scale registry of a Deep Brain Stimulation (DBS) system capable of Multiple Independent Current Source Control (MICC) in the management of symptoms of levodopa-responsive Parkinson's disease (PD).

**Methods:** The Vercise DBS Registry is a prospective, on-label, multi-center, international registry sponsored by Boston Scientific Corporation. The Vercise DBS system (Boston Scientific) is a multiple-source, constant-current system. Subjects were followed up to 3 years post-implantation where their overall improvement in quality of life and PD motor symptoms was evaluated. Clinical endpoints evaluated at baseline and during study follow included Unified Parkinson's disease Rating Scale (UPDRS), MDS-UPDRS, Parkinson's disease Questionnaire (PDQ-39), and Global Impression of Change.

**Results:** To date, 360 patients have been enrolled and this report will provide an overview of data collected so far from implanted patients within this cohort. At 1 year post-implant, 35% improvement in MDSUPDRS III scores (stim on/meds off) compared with baseline was reported. This improvement in motor function was supported by an improvement in quality of life as assessed by PDQ39 Summary Index (4.7-point improvement, n = 193) at 1 year. Roughly 90% of patients and clinicians reported improvement as compared with Baseline. New data collected out to 2 years post-implant will be reported.

**Conclusions:** This DBS registry represents the first comprehensive, large scale collection of real-world outcomes and evaluation of safety and effectiveness of a multiple-source, constant-current DBS system.



OP-03-10

## **2-year follow-up of prospective, double-blinded, multi-center randomized controlled trial evaluating deep brain stimulation with new multiple-source, constant-current rechargeable system for treatment of Parkinson's disease**

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**Objectives:** The objective of the INTREPID clinical trial assessed improvement in motor function and quality of life in patients with advanced, levodopa responsive Parkinson's disease (PD) following bilateral subthalamic nucleus (STN) Deep Brain Stimulation (DBS) using a new device equipped with multiple current sources. In this analysis, 2-year follow-up data will be reported.

**Methods:** INTREPID (ClinicalTrials.gov Identifier: NCT01839396) is a multi-center, prospective, double-blinded, randomized controlled trial (RCT) sponsored by Boston Scientific. Subjects with advanced PD were implanted bilaterally in the STN with a multiple-source, constant current DBS System (Vercise, Boston Scientific). Subjects were randomized to either receive active vs. control settings for 12-week blinded period. Subjects were blinded to treatment assignment and study assessments were administered by a clinician blinded to treatment condition. Motor improvement was evaluated using several assessments including subject motor diaries, UPDRS scores, etc. Assessments for quality of life (e.g. PDQ39) were also administered.

**Results:** The study met the primary endpoint demonstrated by mean difference of  $3.03 \pm 4.52$  hrs. ( $p < 0.001$ ) between active and control groups in ON time w/o troublesome dyskinesia, with no increase in antiparkinsonian medication, from post-implant baseline to 12-weeks post-randomization. At 1-year compared to pre-surgery screening, a 49.2% improvement in UPDRS III scores was reported, and overall improvement in quality of life was maintained. Reporting of 2-year follow-up data is planned.

**Conclusions:** Results of the INTREPID RCT demonstrate that use of a multiple-source, constant-current DBS system is safe and effective for treatment of Parkinson's disease symptoms. This analysis will describe outcomes derived from subjects assessed out to 2-years follow-up.

OP-03-11

**MANAGE-PD: A clinician-reported tool to identify patients with Parkinson's disease inadequately controlled on oral medications - results from vignette-based validation**

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**Objectives:** To evaluate the reliability and validity of MANAGE-PD tool.

**Background:** Timely identification of advancing symptoms of people living with Parkinson's Disease (PD), thereby optimizing their window for utilization for device-aided therapies are areas for clinical practice improvement. MANAGE-PD is a simple clinician-reported screening tool developed to address this practice gap. It is aimed to assist clinicians' decision making for the timely evaluation of PD symptoms.

**Methods:** Hypothetical vignettes (n=10) were developed to represent a wide spectrum of disease severity. A vignette-based validation was conducted via a web-based survey of selected panelists comprised of highly experienced movement disorder specialists (MDS) from US and Europe. A Steering Committee classified each vignette into 3 categories: (i) adequately controlled on oral therapy; (ii) inadequately controlled on oral therapy and recommend oral optimization only; (iii) inadequately controlled on oral therapy and recommend evaluation for device-aided therapies along with oral optimization. Each panelist evaluated one anchor vignette (used for assessing response consistency) and four randomly assigned vignettes using the MANAGE-PD tool. Concordance between clinical judgment for management of patient versus MANAGE-PD recommendation was assessed.

**Results:** The panel included MDS (n=19) from 15 countries, with extensive experience in treating PD [Mean: 24.4±7.6 years; Mean patients treated/month: 73.2±45.4]. In open-ended feedback, panelists reported no issues with usage of the tool. The determination of inadequate symptom control and possible eligibility of device-aided therapies was made based on frequency and severity of motor symptoms, non-motor symptoms and functional limitations. A high concordance between clinical judgement and MANAGE-PD recommendation was observed (Intra-class co-efficient: 0.82; weighted kappa statistic: 0.71; unweighted kappa statistic: 0.78; concordance for the categories ranged from 82.35-88.24%).

**Conclusions:** MANAGE-PD demonstrated high reliability and validity. Future steps include validation with a large global survey of general neurologists and optimizing scoring algorithm based on patient-level data.

OP-03-12

## Long- term effect of deep brain stimulation and continuous infusion of levodopa-carbidopa intestinal therapy on non-motor symptoms in patients with advance Parkinson's disease

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**Objectives:** Our aim was to see long term effects of deep brain stimulation (DBS) and continuous infusion of levodopa-carbidopa intestinal gel (LCIG) on nonmotor symptoms in advanced Parkinson's disease (APD).

**Background:** The modern management of PD is patient-oriented. Nonmotor symptoms influence the most quality of life in APD.

**Methods:** We tested 50 patients before, 1 and 3 years after DBS and 20 patients before and 3 years after LCIG in our Center. The investigation was conducted with anamnesis and treatments' data, Non-motor Symptom Scale (NMSS), Non Motor Symptoms Questionnaire (NMSQ), Visual Analogue Scale (VAS), McGill questionnaire and *Hospital Anxiety and Depression Scale* (HADS), Montreal Cognitive Assessment (MoCA) and Mini Mental State Examination (MMSE), Parkinson's disease sleep scale (PDSS), Unified Parkinson's Disease Rating Scale- part II (activities of daily living-ADL), part III (motor examination -ME), Parkinson's Disease Questionnaire- 39 (PDQ-39) and levodopa dosage. Statistical analysis was done.

**Results:** Mean age was  $71.09 \pm 0.9$  (man 56%; women 44%). Mean disease duration was  $14.0 \pm 0.6$ . We found statistically significant improvement in nonmotor symptoms (NMSS total score and NMSQ), motor symptoms and PDQ-39 in both methods that was persistent and stable after 1 and 3 years. Considering sub-domains, we found significant beneficial effect on sleep, gastrointestinal, cardiovascular and urological symptoms in both methods, but better improvement in pain and sexual function in DBS and mood and apathy section in LCIG patients ( $p < 0.05$ ).

**Conclusions:** We found beneficial and stable effects after 1 and 3 years with both invasive methods (DBS and LCIG) on nonmotor symptoms and quality of life. The most consistent improvements are seen concerning sleep, cardiovascular, gastrointestinal and urological symptoms. This can help us to decide on advanced therapy for individual patients.

## Session IV - Parkinson's disease: Clinical science, therapeutics, surgical management

### OP-04-01

### STN-DBS induced uniform metabolic changes in the globus pallidus, but not in the cerebral cortex: [ $^{18}\text{F}$ ]FDG PET study in Parkinson's disease

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**Background:** Unlike motor symptoms, the effects of STN-DBS on non-motor symptoms are often not predictable. We investigated long-term effects of STN-DBS on the metabolism of the brain in patients with Parkinson's disease (PD) at the individual level. We employed a new method of single-subject statistical parametric mapping (SPM).

**Methods:** We studied 35 patients with PD who received STN-DBS (M/F= 16/19, age=  $56.2 \pm 8.21$ , duration=  $8.77 \pm 3.89$ , mean  $\pm$  SD, years). All subjects were assessed using clinical batteries for motor and non-motor symptoms, and performed [ $^{18}\text{F}$ ]FDG PET before and one-year after STN-DBS. Parkinsonism was assessed at med-off/on prior to STN-DBS, and at med-off/on, and stim-off/on one-year after DBS. Resting [ $^{18}\text{F}$ ]FDG PET was carried out after overnight withdrawal of antiparkinsonian medications. [ $^{18}\text{F}$ ]FDG PET data were analyzed by single-subject SPM using the whole brain as reference.

**Results:** Before DBS, UPDRS III scores were  $51.5 \pm 14.6$  at med off, and  $15.9 \pm 11.7$  at med on ( $p < 0.0001$ ). One year after STN DBS, UPDRS III scores were  $36.1 \pm 17.5$  at med-off/stim-off,  $20.4 \pm 15.4$  at med-off/stim-on,  $15.5 \pm 17.6$  at med-on/stim-off, and  $5.84 \pm 6.6$  at med-on/stim-on. Groupwise SPM analysis comparing post-DBS FDG PET with pre-DBS FDG PET showed significantly increased metabolism only in the medial globus pallidus ( $p < 0.05$ , FDR corrected). Single-subject SPM analysis revealed increases of glucose metabolism with varying extents in the globus pallidus (z-score=  $-0.885 \pm 0.634$  before DBS,  $-0.308 \pm 0.711$  one-year after DBS;  $p < 0.0001$ ). Significant correlation was found between the motor outcomes of STN-DBS and the metabolic increases ( $r = 0.345$ ,  $p = 0.042$ ). On the contrary, glucose metabolism in the cortical regions did not show consistent changes across individuals long after STN-DBS.

**Conclusions:** STN-DBS induced uniform metabolic increases in the subcortical region next to the target, but not in the cortical regions, which in turn correlated with improvement of motor symptoms. These observations explain why STN-DBS does not consistently improve non-motor symptoms, originated from the cerebral cortex.

OP-04-03

## Post-mortem analysis of Parkinson's disease brains after 11 and 12 years of deep brain stimulation of the subthalamic nucleus

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**Objectives:** Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is widely used to alleviate motor symptoms of Parkinson's disease (PD). Through these unique case studies, we aim to describe the fine neuroanatomical and neurochemical alterations that were induced by a chronic stimulation of brain tissue, and to correlate these changes with clinical outcomes and with estimation of current spreading obtained through patient-specific DBS computational modelling.

**Methods:** We provide detailed analysis of 2 PD brains who underwent DBS for 11 and 12 years, the longest STN stimulation periods ever reported in the literature.

**Results:** Clinical data indicate positive outcomes of DBS such as significant reduction of motor symptoms and dopamine medication. As expected, we observed a 300 µm-width gliosis around the implanted electrodes showing high immunoreactivity for GFAP, but also for PCNA and GDNF. In the STN stimulated area only, we identified GFAP+ astrocytes endowed with highly varicose processes that were in close apposition to GLUT1+ blood vessels, potentially involved in decreased permeability of the blood-brain barrier. We also found an increase of the length of GLUT1+ blood vessels in the STN stimulated area, compared to non-stimulated STN regions, the vast majority being immunoreactive for VEGF, indicating an important DBS-mediated angiogenesis. A significant reduction of the number of Iba1+ microglia was also observed near the active contacts, the majority being non-phagocytic, supporting the hypothesis of altered neuroinflammation induced by DBS. The subventricular zone in these particular DBS implanted brains was thicker than in non-implanted PD brains and similar to non-pathological brains matched for age, sex and post-mortem delay, suggesting that DBS may restore normal cell proliferation known to be reduced in PD.

**Conclusions:** With these unique case studies, we hope to reach a better understanding of the long-term cellular and molecular changes induced by chronic DBS.

OP-04-04

## Deep brain stimulation in early-stage Parkinson's disease may reduce the risk of developing dyskinesia

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**Objectives:** To analyze the emergence of dyskinesia after five years in the deep brain stimulation (DBS) in early-stage Parkinson's disease (PD) pilot clinical trial.

**Methods:** The pilot trial was a prospective, randomized, single-blind study that randomized 30 early-stage PD subjects (Hoehn & Yahr II off medications) to receive DBS plus optimal drug therapy (ODT) versus ODT alone (IDEG050016, NCT0282152, IRB040797). Patients were excluded from the trial if they had dyskinesia

or other motor fluctuations. Subjects who completed a five-year follow-up study and who were taking PD medications 6 months - 4 years at enrollment were included in this analysis (n=28). Dyskinesia was considered present if a subject had a score of  $\geq 1$  on UPDRS-IV item 32. Fisher's exact test was used to compare the presence of dyskinesia at five years. Presence and severity of dyskinesia was defined as the sum of UPDRS-IVa (items 32-35). A proportional odds logistic regression model was used with UPDRS-IVa score as the outcome and baseline score, time, and treatment assignment as independent variables.

**Results:** At five years after study enrollment, dyskinesia was present in half of ODT subjects (7/14) compared to only 21% (3/14) of DBS+ODT subjects ( $p=0.24$ ). The odds of developing or worsening dyskinesia (UPDRS-IVa) was nearly 3-fold lower for early-stage subjects who were treated with DBS+ODT versus ODT alone ( $p=0.06$ , OR=0.35, 95% CI: 0.12-1.06).

**Conclusions:** DBS in later PD stages reduces dyskinesia severity, and one hypothesized benefit of applying DBS to stable-responding, early-stage patients is delaying or even preventing the onset of this debilitating effect of levodopa utilization. While the pilot trial was not powered to test that hypothesis, these data suggest that early DBS could reduce the risk of developing dyskinesia. The FDA has approved the conduct of a prospective, multicenter, double-blind, phase III, pivotal trial of DBS in early-stage PD.

#### OP-04-05

### The effectiveness of two-weeks program of self-stretch based on post-isometric relaxation in Parkinson's disease patients

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**Objectives:** Rigidity is one of the primary symptoms of Parkinson's disease (PD). There are various techniques for flexibility improving applied in clinical practice. Post-isometric relaxation (PIR) suggested a highly effective approach of physical therapy (Czaprowski D. et al, 2012). Meanwhile, it is not enough data of muscle self-stretch based on post-isometric relaxation (SSBPIR) in PD patients.

The aim of the study was to evaluate the influence of two weeks of PIR training performed by inpatients autonomously on their joints mobility and balance.

**Methods:** Nine PD patients included in the study had mild to moderate disability and could walk unassisted. They performed SSBPIR training six days a week within two weeks. Basically, the training consisted of 10 exercises all of which included submaximal voluntary static tension for 10 seconds and subsequent 10-15 seconds of static stretching in major joints. All exercises were performed three times consecutively under the certified physical therapist supervision. To evaluate the impact of described above exercises we used the back-scratch and Chair Sit-and-Reach tests and the Berg Balance Scale (BBS).

**Results:** For the tenth session all patients were able to do these exercises independently. The flexibility enhanced in all patients except one (62-years-old woman initially had a low level of mobility). Their levels (n=9) increased significantly ( $p < 0.05$ ) and were as follows: upper limb-left +9.2 cm (3.1-10.1), upper limb-right +8.9 cm (3.4-9.6), lower limb-left +2.8 cm (1.5-4.2), lower limb-right +3.0 cm (1.6-3.9). In contrast, we received no substantial improvement in patients' balance as changes in BBS scores were not significant ( $p=0.14$ ).

**Conclusions:** Self-stretch based on post-isometric relaxation can be considered as an effective method for amelioration of joints mobility, although balance did not increase considerably after these training. The SSBPIR can be applied both inpatients and outpatients.

OP-04-06

## Verbal disruptions in Parkinson's disease spoken discourse as a function of syntax complexity

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**Background:** Cognitive impairments in PD can manifest as language problems (Murray, 2000; Roberts & Post, 2018). Individuals with PD also exhibit higher rates of verbal disfluencies (pauses, reformulations, sound/word repetitions.) Researchers suggest that verbal disfluencies indicate language planning issues in PD (McNamara et al., 1992). However, few studies have directly tested this hypothesis.

**Aim and Objectives:** To evaluate the effects of syntax complexity on the frequency of verbal disfluencies in individuals with PD and healthy controls (HC) during spontaneous speaking tasks.

**Methods:** 19 PD (on-state; H&Y 2-3.5) and 19 HC without MCI/dementia completed a neuropsychology, motor speech, and spoken discourse battery. Language samples were collected using standardized picture sequences. Researchers blinded to group allocation orthographically transcribed and coded samples for verbal disfluencies and syntax complexity (Thompson et al., 1995). Frequency and type of verbal disfluency were analyzed using ANOVAs with group and syntax complexity (whether the disfluency occurred in a simple or complex sentence) as independent variables.

**Results:** There were no group effects on words/minute, total utterances, speech intelligibility, or proportion of complex utterances, suggesting that the two groups did not differ on measures of language productivity or syntax complexity. Groups differed on the proportion of unfilled pauses (PD higher),  $p < .01$ . Both groups produced significantly more revisions, filled pauses ("uhm," "uh"),  $p = .01$ , and sound/word repetitions,  $p = .01$ , in sentences with complex syntax structures. However, the non-significant interaction effect suggests that the impact of syntax planning did not differ between the groups.

**Conclusions:** These results indicate that syntax planning demands affect PD and HC similarly, manifesting as verbal disfluencies vs. as syntax simplification or syntax errors. The clinical and theoretical implications of these findings for PD and typical aging will be discussed. We are currently investigating this aim in 160 PD individuals with and without MCI/dementia (ONDRI trial).

OP-04-07

## Subthalamic deep brain stimulation in Parkinson's disease patient with Othello syndrome

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**Objectives:** Parkinson's disease (PD) may be associated with a wide spectrum of psychiatric symptoms. Delusions are quite rare and commonly related to cognitive deterioration/dementia or dopaminergic treatment. We aimed to describe a PD patient with paranoid jealousy delusion (Othello syndrome/OS) who underwent STN-DBS.

**Methods:** A 65-year-old man with 13-year history of PD was evaluated for DBS-STN. Motor symptoms were relatively compensated on combined antiparkinsonian medication (levodopa/pramipexol/amantadine/rasagiline, LEDD 1600mg). However, pronounced motor and non-motor fluctuations, gait disorders with frequent freezing, and severe OFF-state hypokinesia in the right extremities remained bothersome (UPDRS-3 20; UPDRS-4 9). During the last 5 years, some psychiatric symptoms added (extracampine hallucinations, impulsive-compulsive behavior, apathy). Within 4 months prior operation, patient also developed OS and delusion of poisoning. Considering preserved cognitive function (MMSE 30, MoCA 28, FAB 14) and persisting disabling complications of long-term dopaminergic treatment, patient was assigned for bilateral implantation of STN-electrodes.

**Results:** In early postoperative period, patient developed psychomotor agitation. Psychiatric symptoms increased (visual and auditory hallucinations, delusions of betrayal and persecution). That condition required immediate complete withdrawal of dopamine agonists and lowering of levodopa-dosage. Moderate dose of atypical neuroleptics was prescribed. Activation of STN-DBS was postponed for several weeks until psychotic symptoms resolved. Following STN-DBS, patient experienced stable improvement in OFF-state motor symptoms and decrease in motor fluctuations (UPDRS-3 12; UPDRS-4 1 after 1-year). LEDD could be significantly reduced without deterioration in motor function (450mg/day). There was no recurrence of hallucinatory-delusional symptoms, and neuroleptics were gradually discontinued. Impulsive-compulsive and affective disorders markedly regressed.

**Conclusions:** Our case demonstrates amelioration of OS following STN-DBS. Though psychotic symptoms are traditionally considered a contraindication to surgical treatment, in PD patients with isolated delusions induced by antiparkinsonian medication without marked cognitive impairment, STN-DBS might be considered. To avoid acute psychotic reactions in early postoperative follow-up in these patients, all provocative drugs should be discontinued preoperatively.



OP-04-08

## Pain assessment and pain management study in patients with Parkinson's disease in Uzbekistan

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**Objectives:** Pain syndrome dedicated research on Parkinson's Disease (PD) has not been previously studied before in Uzbekistan. We studied the dependence of the nature of pain on the clinical form of PD and examined the effect of drug treatment of PD on pain syndrome.

**Materials and methods:** There were examined 35 patients with PD in the 1<sup>st</sup> Clinical Hospital of Tashkent Medical Academy. The main group consisted of 25 patients with PD with pain syndrome, the control group consisted of 10 patients.

**Results:** The study showed a direct dependence of the nature of the pain syndrome on the duration of PD ( $g = 0.65$ ;  $p = 0.003$ ). The longer patients suffered from Parkinson's disease, the higher was the likelihood that they had a pain of a central nature. We found a direct dependence of the nature of the pain syndrome on the rate of disease progression ( $g = 0.4$ ;  $p = 0.02$ ). Periarthopathy and spondyloarthrosis were more characteristic for moderate PD progression. Central pain syndrome prevailed in the rapid pace forms of PD. The pain syndrome in PD at any of its stages was affected by anti-Parkinsonian therapy. Pain syndrome on VAS scale decreased by 3 points (50%) ( $p = 0.0015$ ). Motor activity increased by 24 points (50%) ( $p = 0.032$ ), daily activity by 20% ( $p = 0.02$ ), depressive symptoms decreased by 5 points (37%) ( $p = 0.0031$ ).

**Conclusions:** The nature of the pain syndrome depends on the rate of progression, the severity of the disease, the duration of the disease: in the initial stages of PD, myofascial pains are more common, as the disease progresses, they give way to central algorithms mainly on the side of greater motor deficit. Adequate anti-Parkinsonian therapy reduces the severity of pain.

OP-04-09

## Predictive factors of short and long-term outcome of bilateral subthalamic nucleus deep brain stimulation in Parkinson's disease

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**Objectives:** To determine preoperative short- and long-term predictive factors of clinical outcome after bilateral Subthalamic Nucleus Deep Brain Stimulation (STN-DBS) in a large cohort of Parkinson's Disease (PD) patients at the Grenoble University Hospital.

**Methods:** All consecutive PD patients who had bilateral STN-DBS from 1993 to 2010 were retrospectively evaluated pre-operatively (baseline), at one-year (short-term), and up to 17 years (long-term) post-operatively. Demographic variables, brain MRI, and clinical characteristics were collected using medical records. Baseline and short-term evaluations included: the four parts of the UPDRS with subscales in both "defined-off" and "defined-on" conditions, Beck Depression Inventory, Mattis Dementia Rating Scale (MDRS), and Frontal Score. Long-term data included the four parts of the UPDRS in the on-stimulation/on-medication condition. Univariate and multivariate logistic regressions were applied to identify factors associated with a short-term good motor response to stimulation, defined as a postoperative percentage reduction > 25% of the motor UPDRS score in the off-medication condition. Furthermore, univariate and multivariate linear regressions were performed to determine baseline variables associated with long-term motor impairment, quantified through the motor UPDRS.

**Results:** A total of 252 patients were included in the short-term analysis, while a subgroup of 51 patients was further evaluated in the long-term. Male sex ( $P = 0.019$ ), higher baseline MDRS score ( $P = 0.020$ ), and absence of brain MRI ischemic white matter lesions ( $P = 0.032$ ) were predictive factors of short-term good motor response to stimulation. In the long-term, higher baseline Frontal Score ( $P = 0.018$ ) was correlated with lower motor impairment.

**Conclusions:** Baseline cognitive status and white matter ischemic lesions have strong negative impact on the short-term motor outcome in PD patients with bilateral STN-DBS. Frontal lobe dysfunction at baseline represents the main predictor of long-term motor benefit.

#### OP-04-10

### Impact of nordik walking training in patients with Idiopathic Parkinson's disease

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**Objectives:** Nordik walking is a form of physical activity, where, natural walking is enhanced by the addition of the active use of a pair of Nordik walking poles. The objective of this study was to evaluate the effects of 6 weeks of Nordik Walking training on gait rhythmicity, functional mobility, and quality of life (QOL) in patients with mild to moderate Parkinson's disease (PD).

**Methods:** This is an open-labeled experimental pre-post study from October 2016 to December 2018. 860 PD patients walked with Nordik stick (NPD) for 60 minutes during each training session, 8 training sessions a week, for 6 weeks. The other 860 Parkinson patients just walked at equal frequency in the tread-mill (TPD).

**Results:** There was significant effect of intervention in gait speed in group NPD ( $p = 0.001$ ) and but not in group TPD ( $p = 0.096$ ). While there was no significant change in grip strength in Group NPD ( $p = 0.488$ ) and TPD ( $p = 0.852$ ). Incidence of falls was lower in NPD compared to TPD ( $p = 0.001$ ). Mood significantly improved in group NPD ( $p = 0.025$ ) but not in TPD ( $p = 0.091$ ).

**Conclusions:** Nordik Walking provides a simple, pragmatic intervention with efficacy in the management of functionally vulnerable Parkinson patients, and allows their maintained independence. Future studies should replicate this readily applicable intervention in a larger cohort with a longer follow-up period

#### OP-04-11

### Primary health care providers knowledge, attitudes and perceptions of Parkinson's disease in the Kumasi Metropolis of Ghana

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**Background:** Lack of adequate knowledge poses a barrier in the provision of appropriate treatment and care for individuals with Parkinson's disease (PD). Many patients with PD in Ghana are thought to be undiagnosed and untreated, leading to poor health outcomes. Increasing rates of diagnosis and treatment, with consequent improvements in the quality of life of people with PD in Ghana requires an understanding of how PD is perceived and conceptualized amongst the primary health care providers' (PCPs)

**Objectives:** To determine primary health care providers' knowledge, attitudes and perceptions of Parkinson's disease in Kumasi Metropolis

**Methods:** A cross-sectional study was conducted with 178 health workers randomly selected from primary care facilities. Both questionnaire and interview guide were used to gather data. . The questionnaire

covered three domains of PD, including diagnosis, therapeutic options, and disease course. Descriptive statistics and independent sample t-test were used to analyse the quantitative data, while narrative inquiry was used to analyse the qualitative data.

**Results:** The level of knowledge on PD was low, particularly in management (61.4%) and diagnosis (34.4%). Medical officers had significantly higher knowledge scores than the nurses for the whole questionnaire ( $p=0.001$ ), as well as the diagnosis ( $p=0.003$ ) and therapeutic sections ( $p=0.001$ ). Some health workers interpreted PD symptoms as signs of stroke or mental disorder with 23% reluctant to deal with PD patients. Misconceptions amongst PCPs were reflected in the mean (SD) total, diagnosis, therapeutic options, and disease course scores: 13.35 (4.10), 6.82 (1.34), 4.75 (1.14), and 4.19 (1.66), respectively.

**Conclusions:** The results showed that PCPs' baseline knowledge of diagnosis and management of PD and self-perceived knowledge were relatively limited and scored very low. Greatly increased education of PCPs in PD is necessary to improving their ability to accurately diagnose and manage PD patients.

#### OP-04-12

### A blind computerized analysis. Effect of subthalamic deep brain stimulation on posture in Parkinson's disease

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**Introduction:** We sought to assess the effect of subthalamic deep brain stimulation (STN DBS) on Parkinson's disease (PD)-associated postural abnormalities.

**Methods:** A computerized analysis of posture was used to quantify the thoracolumbar, thoracic, and cervical-occipital ventral angles, as well as the thoracolumbar and cervical-occipital lateral angles from the video-repository of three specialized movement disorder centers ( $n = 158$  patients). Data was extracted from frames from video-recordings in the pre-surgical medication-ON (dopaminergic therapy) and post-surgical stimulation-ON/medication-ON states (STN DBS plus dopaminergic therapy). The sum of the five postural angles (global postural angle) was used to compare pre-vs. post-surgical trunk posture alterations. A multivariate analysis was used to examine the association between changes in the postural angles and demographic or clinical variables.

**Results:** There was a 6.7% amelioration in the global postural angle between the pre- and post-surgical assessments ( $p = 0.031$ ). Motor response to and pre-surgical dosage of levodopa, male gender, and shorter PD duration were identified as predictors for posture improvement after STN DBS. Cases meeting criteria for lower ( $n = 2$ ) or upper ( $n = 1$ ) camptocormia respectively improved by 48.1% in the ventral thoracolumbar angle (from  $36.4 \pm 0.0^\circ$  to  $18.9 \pm 4.2^\circ$ ) and 13.8% in the ventral thoracic angle (from  $49.1^\circ$  to  $42.3^\circ$ ). Cases meeting criteria for Pisa syndrome ( $n = 2$ ) improved by 67.5% in the lateral thoracolumbar angle (from  $16.9 \pm 2.0^\circ$  to  $5.5 \pm 4.7^\circ$ ).

**Conclusions:** STN DBS has a relatively small but significant effect on PD-associated postural abnormalities, potentially enhancing the effect of dopaminergic medications alone.

## Session V - Hyperkinetic and Other Movement Disorders

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OP-05-01

### Spasmodic dysphonia as a presenting symptom of spinocerebellar ataxia type 12

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**Introduction:** Autosomal dominant spinocerebellar ataxia type 12 (SCA12) is a rare genetic disorder due to an abnormal CAG repeat expansion (>51 CAG) in the *PPP2R2B* gene. Two SCA12 patients were previously reported from two families coming from Ferrara area, in North-East of Italy. Action tremor of the upper limbs is the most common sign at onset. Subsequently, mild cerebellar dysfunction, hyperreflexia, parkinsonian features, dystonia and dementia can appear. Spasmodic dysphonia has been observed only in two cases of SCA12 and it has never been reported at disease onset.

**Case report:** A 61-year-old woman developed at the age of 50 alteration of voice, followed by head dystonic tremor. Few years later she developed gait instability, mild ataxia and cognitive deterioration. Her paternal aunt died from an unspecified neurodegenerative disorder and two first-degree cousins developed a similar condition in their fifties. Neurological examination showed dystonic tremor of the head and upper limbs, mild left dysmetria, diffuse hyperreflexia and inability to perform tandem gait. Brain-MRI revealed generalized cortical cerebral atrophy particularly evident in the midbrain. Perceptual and acoustic analysis of speech was performed using PRAAT<sup>®</sup>. The patient could not produce sustained phonemic vowel-like sounds or voluntary change voice fundamental frequency. Perceptual analysis showed frequent voice breaks, strained and dysfluent effortful speech production consistent with spasmodic adductor dysphonia. CAG repeats analysis in the *PPP2R2B* gene revealed an expanded heterozygous allele with 61 CAG repeats confirming the diagnosis of SCA12. Trihexyphenidyl (4mg/day) partial ameliorated tremor and dysphonia.

**Conclusions:** SCA12 is phenotypically heterogeneous. Rarely, laryngeal dystonia can be the only sign at onset, making a genetic diagnosis challenging. In the present case, the presence of spasmodic dysphonia along with neurological examination and autosomal dominant family history of neurodegenerative disorders led to the suspicion of SCA12, a condition requiring a multidisciplinary team care.

## OP-05-02

## The effect of repetitive transcranial magnetic stimulation with intensive physical therapy for degenerative cerebellar ataxia: A single-center, single-blinded prospective cohort study

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**Objectives:** To investigate the effect of the combination of repetitive transcranial magnetic stimulation (rTMS) and intensive physical therapy (PT) in the patients with degenerative cerebellar disease.

**Methods:** Ten sessions of rTMS and PT were performed for 2 weeks of hospitalization days. The severity of ataxia was assessed by the International Cooperative Ataxia Rating Scale (ICARS) and secondary outcomes including Mini-mental state examination (MMSE), Beck Depression Inventory (BDI) and Barthel index of Activities of Daily Living (ADL) were investigated before, immediately, 4 weeks and 12 weeks after the intervention.

**Results:** Twenty-three patients were randomized to rTMS group and 22 to the control group. Total ICARS score was decreased in rTMS group, immediately after treatment. This beneficial effect continued 4 weeks after treatment then increased after 12 weeks after treatment ( $p < 0.001$ ). ICARS I ( $p < 0.001$ ), II ( $p < 0.001$ ) and III ( $p < 0.001$ ) score showed similar trend with ICARS total score. BDI of rTMS group were lower than control group during the study period ( $p < 0.001$ ). ICARS IV ( $p = 1$ ), MMSE ( $p = 1$ ) and ADL ( $p = 1$ ) did not statistically differ between the two groups.

**Conclusions:** This study showed that the combination of rTMS and PT improved ataxia symptoms in the patients with degenerative cerebellar ataxia and the beneficial effects were continued for 4 weeks after treatment.

## OP-05-03

## An automated algorithm for detection, quantification and classification of tremor from hand-drawn, pen-on-paper spirals

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**Objectives:** To develop an automated algorithm to detect, quantify and distinguish tremors from pen-on-paper spiral drawings.

**Methods:** Subjects were asked to draw free hand clockwise spirals using the dominant hand on standard pen and paper. Scanned images underwent pre-processing and unravelling of the spiral from Cartesian co-ordinates to radial. Tremor variability (TV) and mean deviation (MD) from a computer generated ideal spiral were computed. For validation, the derived parameters were compared with 1) the Bain and Find-

ley scale (median score of 3 raters) 2) the Fahn-Tolosa-Marin tremor rating scale (FTM) and 3) power of spectrum derived from tri-axial accelerometry. Receiver Operating Curve (ROC) statistics were applied to identify cut-offs to detect tremor spirals from controls. Spiral loop widths were computed to distinguish essential tremor (ET) from dystonic tremor (DT).

**Results:** Hand-drawn spirals from subjects with postural/action tremor (n=38) and healthy volunteers (n=35) were analysed. Both TV and MD showed strong correlation with Bain and Findley ratings (Spearman's correlation: TV,  $\rho=0.55$ ,  $p<0.001$ ; MD,  $\rho=0.56$ ,  $p<0.001$ ). MD correlated strongly with accelerometric power of spectrum for postural tremor (Spearman's correlation for total power: MD,  $\rho=0.47$ ,  $p=0.010$  and for peak power: MD,  $\rho=0.52$ ,  $p=0.003$ ). The FTM total and dominant upper extremity scores did not correlate significantly with TV and MD in patients. Both TV ( $p<0.001$ ) and MD ( $p=0.001$ ) were significantly different between patients and controls. TV was the better parameter to detect tremor (AUC: 0.79, 95% CI 0.67-0.93) with a cut-off value of 35.7 units showing 74% sensitivity and 85% specificity to detect tremor. Spiral loop widths were significantly different between ET (n=19) and DT (n=13) [ $F(1,30)=4.45$ ,  $P=0.043$ ].

**Conclusions:** Automated algorithm derived variables showed good correlation with both Bain and Findley scores and accelerometric recordings of tremor. Algorithm derived variables such as mean loop widths may be useful in distinguishing tremor subtypes.

#### OP-05-04

### SGE-516, an orally-bioavailable neurosteroid, positively modulates GABA<sub>A</sub> receptors and reduces tremor activity in a mouse model of essential tremor

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**Objectives:** The objective of the present study was to test the activity of neurosteroid, SGE-516, at synaptic and extrasynaptic GABA<sub>A</sub>Rs and in a preclinical model of tremor.

**Methods:** Recording of GABA<sub>A</sub>R currents in recombinant cells: Modulation of GABA<sub>A</sub>R currents by SGE-516 was assessed using recombinant  $\alpha 1\beta 2\gamma 2$  (representative synaptic) and  $\alpha 4\beta 3\delta$  (representative extrasynaptic) GABA<sub>A</sub>Rs expressed in LTK and CHO cells, respectively. Recording of GABA<sub>A</sub>R currents cerebellar slice: Modulation of extrasynaptic (tonic inhibition) and synaptic (phasic inhibition) GABA<sub>A</sub>R currents was assessed using whole-cell voltage clamp recordings in rat cerebellar granule cells. Baseline-normalized changes in holding current and inhibitory postsynaptic current decay were measured following application of 0.05, 0.1, and 1  $\mu$ M SGE-516.

Measuring harmaline-induced kinetic tremor in mice: Harmaline (10 mg/kg, i.p.) tremor was measured in mice using a piezoelectric (PZ) plate. Vehicle or SGE-516 (0.3, 1, 3 mg/kg, i.p.; n = 15 mice/ group) was administered 30 min prior to harmaline administration. PZ power was measured for 20 min following harmaline administration. Frequency power histograms were constructed and differences between treatment groups were assessed.

**Results:** SGE-516 positively modulated both synaptic and extrasynaptic GABA<sub>A</sub>R in heterologous cells. Additionally, SGE-516 increased both synaptic and extrasynaptic GABA<sub>A</sub>R currents in cerebellar granule cells. SGE-516 (1.0 mg/kg, i.p.) led to a significant reduction of peak harmaline response between 10-20Hz ( $51.5 \pm 13.6\%$  (mean  $\pm$  sem) reduction,  $p < 0.005$ , one-way ANOVA, Holm-Sidak's multiple comparison test) and a reduction of PZ power relative to harmaline across time.

**Conclusions:** The orally bioavailable (rat %F = 25%) neurosteroid, SGE-516, is a positive modulator of both synaptic and extrasynaptic GABA<sub>A</sub>R and is effective in a preclinical model of tremor. By modulating network excitability in a manner distinct from historical GABAergic treatments (e.g. benzodiazepines), it is hypothesized that neurosteroid GABA<sub>A</sub>R modulators may also have a therapeutic potential beyond seizure disorders.

#### OP-05-05

### Comparison of botulinum toxin injections in forearm FLEXor plus EXtensor muscles versus flexor muscles alone for the treatment of essential hand tremor (FLEX-D ET)

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**Background:** Essential tremor (ET) is one of the most common movement disorders affecting 4% of adults of 40 years of age and older. Botulinum toxin (BoTN) studies have shown improvement in tremor severity but no improvement in quality of life.

**Methods:** This was a 12-week pilot randomized (1:1 ratio), double-blind, placebo controlled study of 21 patients with ET. Patients were randomized to receive either injections of 150 units of abobotulinumtoxinA (Dysport®) in flexor compartment of dominant arm (75 units in flexor carpi radialis [FCR] and 75 units in flexor carpi ulnaris [FCU]) along with placebo in extensor carpi radialis (ECR) and extensor carpi ulnaris (ECU) or 75 units in FCR and FCU and 25 units in ECR and ECU. Response was measured using Tremor Rating Scale. Quality of life measurements were evaluated by QUEST questionnaire for ET. In addition, patients completed a Task Specific Improvement Scale. The same scale was used to measure patient's overall functional improvement, which we called PGI-VAS. Clinicians were asked to complete the same scale.

**Results:** As a whole, the group significantly improved in TRS ( $p < .001$ ) and a mildly significant decline in grip strength ( $p < 0.001$ ) with a decrease by 38% in flexor+extensor group and 30% in flexors only group. There was no significant change in any of the other measures. Symptom worsening was not reported in any patient.

The flexor + extensor group scored significantly higher on the CGI-VAS ( $p = .025$ ).

**Conclusions:** From our small pilot study, it does appear that the group who received flexor and extensor injections experienced greater benefit without additional worsening of grip strength, as compared to those who had flexor only injections. Using this protocol regimen as a treatment option for future larger clinical trials is worth considering.



OP-05-06

## Treatment of tremor with botulinum toxin

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**Objectives:** Adequate management of tremor has been an unmet need in clinical practice. Most of the anti-tremor medications have limited efficacy and are associated with undesirable adverse effects, especially in elderly patients. Several studies have reported good outcomes with the use of botulinum neurotoxin (BoNT) for the treatment of tremor (Mittal et al, 2019). We systematically reviewed published studies of BoNT in the management of tremor.

**Methods:** A PubMed search was performed in January 2019 using the terms "botulinum toxin" and "tremor" with additional search terms "essential tremor", "Parkinson's disease", "multiple sclerosis", "writing tremor", "dystonic tremor", "rubral tremor", "voice tremor" and "cerebellar tremor".

**Results:** This search yielded 659 articles and 36 articles were included for this review.

We found a total of ten published studies evaluating the role of BoNT in essential tremor patients with hand tremor (3 randomized controlled studies [RCT] and 7 open-label studies [OL], seven studies on PD tremor (1 RCT and 6 OL), seven studies on voice tremor (7 OL), two studies on hand tremor in multiple sclerosis (1 RCT and 1 OL), two studies on head tremor in essential tremor (1 RCT and 1 OL), one OL study on dystonic head tremor, two OL studies on essential palatal tremor, two OL studies on task-specific hand tremor (primary writing tremor and musician tremor). There is one OL study on each proximal upper limb tremor and jerky position-specific upper limb tremor.

**Conclusions:** Results of these studies suggest that clinically meaningful improvement in hand tremor can be achieved with BoNT therapy. Additionally, BoNT has been reported to be efficacious in alleviating head and palatal tremor, tremor in multiple sclerosis, and proximal positional tremor.

### References:

1. Mittal SO, Lenka A, Jankovic J. Botulinum toxin for the treatment of tremor. *Parkinsonism Relat Disord.* 2019 Jan 26. pii: S1353-8020(19)30023-9.

OP-05-07

## Cerebellar peduncle atrophy in essential tremor: Another piece of the puzzle?

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**Objectives:** Subtle cerebellar signs are frequently observed in essential tremor (ET) and neuropathological and neuroimaging studies suggest the possibility of cerebellar dysfunction in ET. This study aims to evaluate the macrostructural integrity of the superior, middle and inferior cerebellar peduncles (SCP, MCP, ICP) and cerebellar gray and white matter (GM, WM) volumes in patients with ET, and compare these volumes between patients with and without cerebellar signs (ETc, ETcn).

**Methods:** 40 patients of ET and 37 age and gender matched healthy controls were recruited. Atlas-based region of interest analysis of the SCP, MCP and ICP and automated analysis of cerebellar GM and WM volume was performed.

**Results:** Significant atrophy of bilateral MCP and ICP, and atrophy of bilateral cerebellar GM was observed in ET. Cerebellar signs were present in 20% of subjects with ET, and atrophy of right SCP, bilateral MCP, ICP and left cerebellar WM was observed in the ETc subgroup in comparison to ETcn.

With the exception of a negative correlation trending toward significance between right ICP volume and total FTMRS score ( $r=-0.302$ ,  $p=0.058$ ), and between right GM volume and right FTMRS score ( $r=-0.312$ ,  $p=0.05$ ) no other significant correlations were observed between the volumes and duration of illness or FTMRS scores.

**Conclusions:** Patients with ET have significant atrophy of cerebellar peduncles, particularly the MCP and ICP, with additional atrophy of the SCP observed only in the ETc subgroup. These abnormalities may contribute to the pathology in ET and form an essential component for the pathogenesis of cerebellar signs in ET.

OP-05-08

## Precise surface positioning of the obliquus capitis inferior muscle

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**Objectives:** To clarify surface positioning of obliquus capitis inferior (OCI) muscle and provide accurate puncture path for botulinum toxin (BTX) injection in cervical dystonia (CD) patients.

**Methods:** Firstly, reconstruction of OCI was performed in 17 CD patients who underwent cervical CT scan. Surface projection of the start and stop points of OCI was found and the relationship between OCI and surface markers was analyzed. Secondly, 10 healthy volunteers were examined by B-ultrasound to determine the thickness and depth of OCI and the distribution of adjacent muscles and blood vessels. Finally, 20 CD patients with OCI spasm were injected with BTX under electromyography guidance using the puncture path summarized from above data.

**Results:** OCI was located at the oblique transverse plane between spinous process of axis (C2) and tragus of the same side. The surface distance between C2 spinous process and tragus was  $13.58 \pm 0.98$  cm. The surface distance between C2 spinous process and transverse process of atlas (C1) was  $4.13 \pm 0.54$  cm. The surface distance between C2 spinous process and the midpoint of OCI was  $2.55 \pm 0.27$  cm. B-ultrasound showed that OCI was covered by semispinalis capitis muscle (SECM), under OCI was the atlantoaxial joint and the vertebral artery was located at the superior lateral part of OCI. The thickness of OCI was  $4.32 \pm 1.18$  mm and its depth was  $20.11 \pm 3.88$  mm. We suggested the injection path for OCI as follow: the puncture site is the inner 1/5 between C2 spinous process and tragus. The needle is inserted along the sagittal plane and passes through trapezius, splenius capitis and SECM. B-ultrasound confirmed that BTX was successfully injected into OCI using this puncture path in all the 20 CD patients.

**Conclusions:** We suggested a useful and precise surface positioning method and puncture path for OCI.

#### OP-05-09

### Plantar grasp sign as a screening tool for orthostatic tremor

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**Objectives:** Orthostatic tremor (OT) is a rare neurological disorder characterized by a sensation of instability while standing. Beyond mild to moderate global ataxia and the helicopter sign, very few clinical signs have been described for OT to date. Finding other accurate and reliable symptoms and signs could prove valuable for OT recognition and diagnosis.

**Methods:** This protocol is part of the University of Nebraska Medical Center Orthostatic Tremor longitudinal study. It was noted that OT patients flex their toes and sometimes the foot arch while standing. They stated that they would do this to “grab” the floor, and some felt better by doing so. Therefore, every participant was asked the following question regarding this plantar grasp: “Do you curl your toes to “grab the floor” when you are standing still?”.

**Results:** There were 34 OT patients (mean age= 68.5, 88% females), and 20 controls (average age=69.4, 65% females). Average disease duration was 18 years. Eighty-eight percent of patients with OT had plantar grasp sign and none of the controls. The Plantar Grasp Sign was found to be very sensitive (88%), and extremely specific (100%) in our cohort. Non-weighted Negative Likelihood Ratio (NLR) was 0.12, but the 3% prevalence-weighted NLR was so low that the negative post-test probability was close to zero.

**Conclusions:** Due to its high sensitivity, specificity, and ideal likelihood ratio, we propose that the Plantar Grasp sign should be incorporated as part of the diagnostic tools in assessing the patients with possible Orthostatic Tremor. Ascertainment of this sign on patients with symptoms concerning for OT should prompt confirmatory testing.

## OP-05-10

**Development of orthostatic tremor screening questionnaire (OTSQ)**

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**Objectives:** Orthostatic tremor (OT) patients are commonly undiagnosed or misdiagnosed for years. The gold standard test for orthostatic tremor (OT) is the presence of a 13-18 Hz tremor in the legs on surface electromyography (sEMG) while standing. We have developed the OT Screening Questionnaire (OTSQ) to determine which patients should be sent for confirmatory EMG.

**Methods:** This is part of the University of Nebraska Medical Center OT longitudinal study. Multiple OT experts and patients were interviewed, and survey items were chosen and reviewed for clarity. Cognitive pretesting then followed, gathering understanding and opinions about each item from real patients in a life interview. OTSQ has designed with 4 yes/no questions in a flowchart. The gold standard was the EMG confirmation of OT.

**Results:** OTSQ was prospectively administered to 34 OT subjects (mean age=68.5, 88% females) and 20 controls (mean age=69.4, 65% females). Average disease duration was 18 years.

About half of the patients (47%) were taking medications for OT. OTSQ flowchart was 100% sensitive and specific for this pre-selected group of OT subjects and healthy controls.

Each of the four questions has a sensitivity of 100%, and when all four are combined the specificity is very high as well.

**Conclusions:** OTSQ is a highly sensitive tool and could be a useful diagnostic screening test for OT. Sensitive screening tools could avoid unnecessary testing on patients unlikely to have OT, while increasing the likelihood of capturing all patients with the disease. Additional validation of this tool in a population of subjects with unsteadiness due to many different etiologies is underway to ensure its usability.

## OP-05-11

**Prediction of fall among patients with Parkinson's disease: A cross sectional study, India**

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**Objectives:** As per systematic review, the contribution towards Parkinson's patients in association with fall prediction from an Indian community is nowhere found in the literature. This cross sectional study aimed to identify the risk factors that lead to fall among patients with Parkinson's disease, assess the stage of severity; its contribution to fall and also predict fall among the patients.

**Methods:** 94 patients diagnosed with Parkinson's disease were included using convenience sampling from Ernakulam district of Kerala and Bangalore district of Tamil Nadu, India. A semi-structured questionnaire was employed to understand the demographics, risk factors, disease severity, balance and level of

functioning using Hoehn-Yahr scale, Berg Balance scale and Activities-Specific Balance Confidence scale respectively. Advanced statistical methods including regression, logistic regression and multivariate analysis of variance were employed to generate the results.

**Results:** Level of functioning assessed through ABC score and severity of disease were found to be the strongest contributing risk factors of fall among the participants ( $p < 0.001$ ). Using Multivariate Analysis of Variance we conclude that there is a significant difference in the average mean Activities-Specific Balance Confidence score from 52.45 to 28.57 when patient proceeds to stage 3 (mild to moderate bilateral disease) from stage 2.5 (mild bilateral disease with recovery on pull test) according to Hoehn and Yahr staging. Activities-Specific Balance Confidence score which reflects the level of functioning was found to be the variable used for prediction of fall.

**Conclusions:** A simple Activities-Specific Balance Confidence scale could be employed by practitioners to predict fall risk among the patients. The findings emphasize the necessity for an effective awareness regarding the stage transition where there is a high risk of fall, among physicians and care takers. Understanding the high risk severity stage transition would help tailor fall prevention program and can further reduce the risk of other post fall fatalities.

#### OP-05-12

### Differential transcription analysis reveal specific expression pattern and disease associated new biomarkers in child Friedreich's ataxia patient

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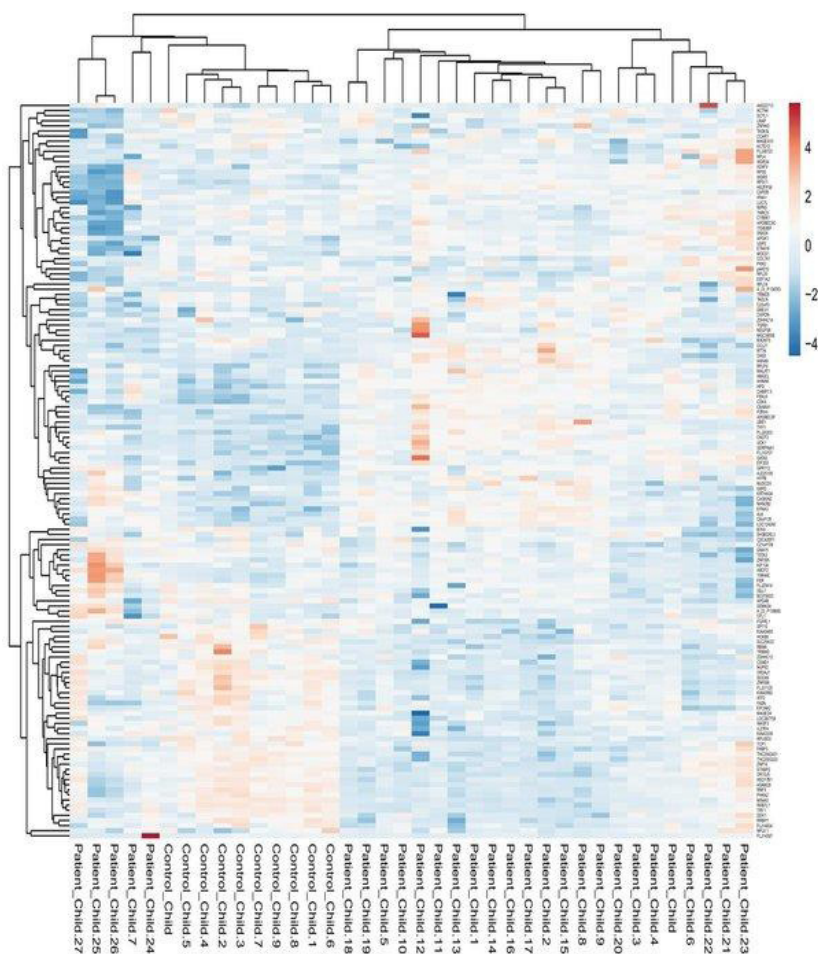
**Objectives:** Reduced expression level of *FXN* is reported to be major reason for *Friedreich's ataxia* (FRDA). However, other differentially expressed genes may also disturb cell harmony leading to disease pathophysiology. Therefore, we performed genome wide expression analysis to explore blood based biomarkers associated with FRDA and tried to explore pathophysiological insights of disease.

**Methods:** The genome wide expression data of control individuals ( $n = 10$ ) and FRDA patients ( $n = 28$ ) were extracted from the public Gene Expression Omnibus (GEO) database that are under the series ID GSE11204 (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE11204>). The R-package, "limma" (<https://bioconductor.org/packages/release/bioc/html/limma.html>) was utilized for the mRNA expression calculation. Further to extract the differentially expressed genes in FRDA, unpaired Student t-test and bonferroni test was applied. The ontology analysis of significantly altered genes was done using String Database (string-db.org). The DisGeNET database (<http://www.disgenet.org>) was also used to find the FRDA associated genes.

**Results:** In FRDA phenotype, 68 genes were found to be up-regulated and 76 were down-regulated significantly ( $p < 1.0E-06$ ) (Figure 1). It is also interesting to note that the identified genes were not reported earlier as compared to the FRDA gene list provided at DisGeNET database. Genes were mainly associated with metabolic processes such as cellular metabolism of the transition metal, lipid metabolism,

etc (Table 1). The gene set enrichment and network analysis suggested that deregulated genes were mainly leading to altered metabolic processes damage and affect tissues leading to neuro- and cardio-degeneration.

**Conclusions:** The *in-silico* analysis identified specific pattern of differentially expressed genes that were found to be associated with metabolic processes and its deregulation may lead to neuro and cardio degeneration in peripheral blood monocyte samples of FRDA patients. These genes may provide new insights in disease etiology as well as new predictive value in therapeutics.



[Figure 1: Heatmap of mRNA expression of significantly altered 144 genes in GSE11204 dataset. Clustering the samples using -means revealed two groups, FRDA child patients (n=28) and normal children (n=10).]

# POSTER EXHIBITION

## Topic: Parkinson's disease - Basic science and genetics

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P 001

### The role of glutamate co-transmission by serotonin neurons of the dorsal raphe nucleus in the regulation of motor behavior and L-Dopa-induced dyskinesia

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**Objectives:** Parkinson's disease (PD) is characterized by the progressive loss of midbrain dopaminergic (DA) neurons that innervate the striatum. The DA precursor L-3,4-dihydroxyphenylalanine (L-Dopa) is the most effective pharmacotherapy for PD but its chronic use is hampered by adverse effects such as abnormal involuntary movements (AIMs) termed L-Dopa-induced dyskinesia (LID). Recent studies have shown the crucial role of serotonin (5-HT) neurons in LID expression. Through this study, we aim to specifically address the functional role of glutamate co-transmission by 5-HT neurons of the dorsal raphe nucleus (DRN) in the regulation of motor behavior and in LID expression.

**Methods:** We used the CRISPR-Cas9 technology, allowing a region and neuron-specific conditional knock-out, in adult mice. We injected an AAV encoding guides RNA for the atypical vesicular glutamate transporter 3 (*vglut3*) gene in the dorsal raphe nucleus (DRN) of transgenic ePet-cre+/Cas9flox+ mice, in order to knock-out the expression of *vglut3* specifically in 5-HT neurons of the DRN. After extensive behavioral testing, these mice were injected with 6-OHDA in the medial forebrain bundle to selectively lesion DA axons, and then with L-Dopa, to induce AIMs.

**Results:** RT-qPCR assay, RNAscope and immunohistochemistry confirm the depletion of VGLUT3 in AAV-infected 5-HT neurons of the DRN. High-resolution confocal analysis of target sites reveals a decreased number of axon varicosities emitted by VGLUT3-depleted 5-HT neurons. Before DA lesion and L-Dopa administration, VGLUT3-depleted mice show increased spontaneous motor activity, high level of anxiety and anhedonia. Compared to controls, VGLUT3-depleted mice show similar motor disabilities induced by 6-OHDA and a trend towards exacerbated involuntary movements induced by L-Dopa treatment.

**Conclusions:** VGLUT3 that is co-released by 5-HT neurons of the DRN appears to be involved in the regulation of anxious and spontaneous motor behaviors as well as in rewards. Our preliminary results also suggest a role in the expression of LID.

P 002

**Synuclein Alpha's variant, rs 894280 affects cognition in PD patients**

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**Objectives:** To assess the effect of rs894280 of *Alpha-synuclein(SNCA)* gene on cognitive profile of idiopathic Parkinson's disease (PD) patients and patterns of neuronal activity during a set-shifting task

**Methods:** 97 participants were recruited including 60 PD patients (Hoehn & Yahr stage II/III) and 37 age-matched neurologically Healthy Controls (HC). Genotyping was performed by TaqMan assay (8933128-10). All participants had a comprehensive assessment of the five main cognitive domains (executive-function, language, memory, attention and visuo-spatial). Each individual had one structural and functional MRI scan in a 3T GE scanner. During the scan participants completed three runs of the Wisconsin-Card-Sorting-Task (WCST). FMRIB Software Library was used for data analysis.

**Results:** One outlier was removed from each group. Regression test showed a significant association between the major allele (CC) and average z-scores of the following cognitive domains in the PD group: memory (n=59, R=0.302, p=0.02), and attention (n=59, R=0.289, p=0.027). Homozygous-CC patients had a significant trend for higher MoCA scores compared to homozygous-TT patients (n=59, Mann-Whitney U test p=0.057). No significant association was found for cognitive data in HC.

Homozygous-CC patients showed higher activity during planning a set-shift in Posterior Cingulate, Precuneus and Superior Temporal regions compared to homozygous-TT patients. During set-shifting homozygous-CC patients showed higher activity than heterozygous carriers in bilateral Dorsolateral Pre-Frontal Cortex, Precuneus and Posterior Cingulate Cortex. These results reflect previously reported differences between patients with Mild Cognitive Impairment (PD-MCI) and patients without Mild Cognitive Impairment (PD-nonMCI). Intragroup analysis showed decreased activity during WCST as the number of C alleles was reduced (CC>CT>TT).

**Conclusions:** *SNCA*rs894280 has a specific impact on attention, memory, and neuronal activity during executive processes in PD patients but this is not the same for HC. Further studies with increased participant numbers are necessary to validate these results.



P 004

## Neuroinflammation genomic markers in genome-wide association study of Parkinson's disease

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**Background:** Neuroinflammation may contribute to the pathogenesis of neurodegeneration in Parkinson's disease (PD) because inflammation is a neuropathologic feature of patients with PD and it has been reported in experimental models of PD. However, the roles of genes related to inflammation in the development of PD has been unclear.

**Objectives:** We aimed to investigate the association between genetic variants related to neuroinflammation and the risk of PD.

**Methods:** Study subjects included patients with PD (N=1,070) and healthy controls (N=5,000) who were unrelated and ethnic Koreans. Genomic data was produced by the Korean Chip (K-CHIP), Affymetrix Axiom KORV1.1 (variants number of 827,400), which contains the imputation GWAS grid (505,000 Asian-based grid), functional variants of nonsynonymous exome content (84,000 Korean-based grid and 149,000 cSNPs and InDels selected from 2,000 whole-exome sequencing and 400 whole-genome sequencing data that are polymorphic in Korean), pharmacogenetics variants, variants in genes involved in absorption, distribution, metabolism and excretion (ADME) of drugs, and expression quantitative trait loci (eQTL). Genomic analysis was performed after stringent sample and SNP quality controls. Genetic variants related to neuroinflammation were selected and specifically analyzed in PD cases and controls.

**Results:** The *HLA-ASNP* rs12665039 the most significant association with PD (OR=1.28, CI=1.15-1.44,  $P=1.89 \times 10^{-5}$ ). The *HLA-DOBSNP* rs2071469 was the second most significant loci (OR=0.83, CI=0.75-0.91,  $P=1.72 \times 10^{-4}$ ). Other variants in Chromosome 6 and 11 showed nominally significant associations with PD, but those did not remain significant after Bonferroni correction.

P 005

## Variants in the beta-Glucocerebrosidase A (GBA) gene in German patients with Parkinson's disease

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**Objectives:** *GBA* encodes the lysosomal enzyme beta-glucocerebrosidase A. *GBA* mutations cause the lysosomal storage disorder Gaucher disease (GD, types 1, 2 and 3) and have been found to increase the risk of Parkinson's disease (PD), reduce age at PD onset and increase the risk of neuropsychiatric manifestations in patients with PD. In fact, *GBA* polymorphisms are the largest risk factor for idiopathic PD identified to date. Heterozygous *GBA* mutation carriers have a risk of 10-30% to develop PD by age 80 years, corresponding to a 20-fold increase versus non-carriers; 5-25% of non-familial patients with PD carry

*GBA* variants. *GBA* variants have been shown to be associated with a distinct cognitive profile in cognitive impairment in PD (prevailing deficits in working memory, executive function and visuospatial abilities). It was the aim of this study to characterize *GBA* variants (mutations and polymorphisms) in a cohort of German patients with PD.

**Methods:** We performed whole-genome sequencing of the *GBA* gene (11 exons; NP\_000148.2) using DNA samples of 332 German patients with PD (primer sequences available upon request). All patients were Caucasian; 32% had a positive family history.

**Results:** All 11 *GBA* exons were sequenced (100% coverage). We found *GBA* variants in 44 out of 326 German patients (13.5%), including 13 non-synonymous variants (one of them being novel), three synonymous variants, one nonsense variant (exon 8), as well as one deletion (exon 1). We present data including minor allele frequencies and in silico pathogenicity analyses for all variants identified. Six patients were heterozygous and two patients were homozygous for the E365K polymorphism. The N370S mutation was not found.

**Conclusion:** Here we report detailed results of whole-genome sequencing of the *GBA* gene in a large cohort of German patients with PD. *GBA* variants were frequent in our cohort of German patient with PD.

## P 006

### Finding shared biological pathways between inflammatory bowel disease and Parkinson's disease using large-scale gene expression data

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**Objectives:** Inflammatory bowel disease (IBD) is an epidemiological risk factor for developing Parkinson's disease (PD). In addition, there is genome-wide pleiotropy between the two disorders. Nonetheless, it is unclear through which biological mechanisms IBD and PD are related. Here, large-scale gene expression data was used to reveal shared biological pathways between IBD and PD.

**Methods:** Gene expression data from 31,499 publicly available RNA-seq samples was used for a guilt-by-association analysis between genes associated with IBD and genes associated with PD. The eigenvectors of the first 307 principal components of the RNA-seq data were used to correlate expression data of the selected genes on the basis of which the genes were clustered. Functional enrichment of the discovered gene clusters was subsequently performed using the ToppGene Suite to reveal which biological pathways underlie the observed correlation in expression levels.

To assess the specificity of the revealed biological pathways for the association between IBD and PD, the same analyses were performed using genesets associated with Rheumatoid Arthritis (RA) and Alzheimer's Disease (AD) as a control for IBD and PD respectively.

**Results:** The results from the clustering analysis as well as the functional enrichment analysis, comparing IBD and PD genesets, will be presented. Furthermore, the results from both control states, comparing RA and PD genesets, as well as IBD and AD genesets, will be presented to indicate the specificity of the shared biological pathways for the genetic and epidemiological relationship between IBD and PD.

**Conclusions:** Functional enrichment analysis, here used to correlate gene expression data of genesets associated with IBD and PD, can be a useful method to reveal shared biological mechanisms between the two disorders that can guide the translation from genetic and epidemiological associations to causal relations between the two disorders.

P 007

### **Associations of 18 microtubule associated protein tau (*MAPT*) H1 subhaplotypes and the H2 haplotype with clinical features of Parkinson's disease**

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**Objectives:** The aim of this study was to assess associations of microtubule associated protein tau (*MAPT*) (sub-)haplotypes with clinical features in patients with Parkinson's disease (PD).

**Methods:** We included 856 Caucasian patients with PD, who were seen at the Mayo Clinic Florida and had no known mutation causing PD. We retrospectively analyzed charts and extracted the following clinical and demographic information: age at PD onset, sex, disease duration, rate of disease progression, survival after PD onset, levodopa use, levodopa response, bradykinesia, rigidity, postural instability, resting tremor, postural tremor, dementia, dystonia, dyskinesia, autonomic dysfunction (gastrointestinal and urogenital), impulse control disorder, (pseudo-)hallucinations, depression, orthostatic hypotension, REM sleep behavior disorder (RBD), restless legs syndrome (RLS), and PD subtype (akinetic-rigid, tremor-dominant, gait difficulty, or mixed).

**Genetic analyses:** Six *MAPT* variants tagging H1 subhaplotypes (rs1467967, rs242557, rs3785883, rs2471738, rs7521) and the H2 haplotype (rs8070723) were genotyped using TaqMan SNP genotyping assays (QuantStudio 7 Flex Real-Time PCR system, Applied Biosystems). Genotype call rates were 100% for each variant. Associations were calculated for the 19 *MAPT* (sub-)haplotypes seen in >1% of patients.

**Results:** Significant associations ( $P < 0.0021$ ) were observed between the H1b subhaplotype and a higher likelihood of orthostatic hypotension (OR=1.72); H1j and a lower likelihood of resting tremor (OR=0.14) and a higher likelihood of RBD (OR=3.21); H1r and a lower likelihood of bradykinesia (OR=0.14); H1v and a higher likelihood of RLS (OR=5.49). Additionally, suggestive associations ( $P < 0.01$ ) were noted for H1b (dyskinesia), H1f (dystonia and hallucinations), and H1v (depression). The strongest associations of the H2 haplotype were seen with dystonia (OR=1.61,  $P=0.015$ ) and the mixed PD subtype (OR=1.46,  $P=0.038$ ); they did not reach levels of significance.

**Conclusions:** Several *MAPT* H1 subhaplotypes (H1b, H1j, H1r, and H1v) were significantly associated with specific clinical features seen in PD (orthostatic hypotension, resting tremor, RBD, bradykinesia, and RLS).

P 008

### **$\alpha$ -synuclein transmission activates the MAPK signal pathway in dopaminergic neuron by inhibiting the conjugation of *Sema6D* and Plexin B**

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$\alpha$ -synuclein was defined as a "prion-like" agent transferred from cell to cell in Parkinson's disease pathology. The recipient neurons suffer from amyloidogenic proteins aggregation, neuroinflammation, endoplasmic reticulum stress, mitochondrial dysfunction and apoptosis. And MAPK signal pathway has been proved to play a vital role in some of these pathological process.

Our microarray analysis data indicated that exogenous  $\alpha$ -synuclein could inhibit the expression of some members of *SEMA* family, such as *SEMA4D*, *SEMA3F*, *SEMA6D*, *SEMA7A*. The subsequently research illustrated that the gene expression and protein translation of *SEMA6D* were decreased consistently after  $\alpha$ -syn stimulation. What's more, the conjugation between *Sema6D* and its binding membrane protein, Plexin B, was suppressed by exogenous  $\alpha$ -syn treatment. And the MAPK signal pathway was activated when the gene of *SEMA6D* was silenced and the conjugation between *Sema6D* and Plexin B was declined.

The results above supported the hypothesis that exogenous  $\alpha$ -syn might activates the MAPK signal pathway and induced the neuron death by regulating the expression of *SEMA6D* and declining its binding to Plexin B.

P 009

### **In vivo and In vitro study of 17 $\beta$ estradiol against amyloid beta neurotoxicity in synaptosomes of aging rats: A therapeutic drug for Parkinson's disease**

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**Objectives:** The aim of the present study was to determine the effects of neuropeptide, neurokinin B (NKB) and amyloid beta fragment A $\beta$  (25-35) on 17 $\beta$  estradiol (E2) treated aging female rat brain of 3 months (young), 12 months (adult) and 24 months (old) age groups.

**Methods:** The aged rats (12 and 24 months old) were given subcutaneous injection of E2 (0.1  $\mu$ g/g body weight) for 30 days. Synaptosomes were incubated with NKB, A $\beta$  (25-35) and NKB+ A $\beta$  (25-35) in a microfuge tubes at 37°C for 60 min in a shaking water bath with 0.1, 1 and 5  $\mu$ M concentration of each of the peptides in all age groups of control and E2 treated rats. The learning and memory function were assessed by Morris water maze test. The mRNA and protein levels of PPAR $\gamma$  were evaluated by real time (RT)-PCR and Western blot analysis.

**Results:** The results obtained in the present work revealed that increased activities of antioxidant enzymes (glutathione reductase, superoxide dismutase and decrease in calcium levels, acetylcholinesterase (AChE) activity, neurolipofuscin accumulation and malondialdehyde (MDA) in presence of NKB and combined

NKB and A $\beta$  in vivo E2 treated aging rat brain. An *in vitro* incubation of E2 treated synaptosomes with A $\beta$  showed toxic effects on all the parameters, while NKB showed stimulating effects and the combined NKB and A $\beta$  showed a partial effects as compared to A $\beta$  (25-35) and NKB alone. Similar results were obtained with the increased antioxidant enzymes levels, improved learning and memory performances, reduced AChE activity and MDA levels, significantly increased PPAR $\gamma$  expression, and alleviated TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 compared with the E2 treated aging rat hippocampus.

**Conclusions:** Present study elucidates an antioxidant, anti-aging and neuroprotective role of tachykinin peptide NKB against the beta amyloid induced toxicity in E2 treated female rats.

## P 010

### The effect and feature on mitochondria of Parkinson's disease-related genes - PINK1, Parkin, and CHCHD2

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The purpose of this study is to understand the change of mitochondria morphology for some genes to cause young onset familial Parkinson's diseases using drosophila.

We would study PINK1 knock-out, Parkin knock-out and dCHCHD2 knock-out in normoxia or hypoxia condition.

In cellular level, Parkinson's disease (PD) has prominent mitochondrial dysfunction. PINK1 and Parkin, which encode mitochondrial protein kinase and cytosolic ubiquitin (Ub) ligase, relatively, were identified as the genes responsible for the autosomal recessive form of juvenile Parkinson's disease. The newly identified PD-related gene CHCHD2, which encodes a mitochondrial protein, was one of etiologies of PD. The loss of CHCHD2 in *Drosophila* causes abnormal matrix structures and impaired oxygen respiration in mitochondria, leading to oxidative stress.

From this study, we found that hypoxia caused moderate to severe damage on mitochondria. Under 8~10% O<sub>2</sub> concentration, normal control (UAS-Mito GFP/+; MHC-GAL4/+) showed mild deformity of mitochondria with reduced GFP (green fluorescent protein) signal but expressing normal myofibrils. And Parkin knock out (MHC-Gal4, UAS-mito GFP/+; dPark [25]/dPark [1]) made big mitochondrial clumps and depicted GFP signal might be reduced. Also, PINK1 knock out (B9/y;; MHC- mito GFP) demonstrated severe deformity of mitochondria and various mitochondrial clumps such like fusion and fission. Furthermore, GFP signal is reduced. Finally, CHCHD2 knock out made an expression of moderate deformity of mitochondria such as fission or defragmentation under normoxia pressure.

In this study, we a little understood the physiological and pathological roles of PINK1, Parkin and CHCHD2. Also, CHCHD2-deficiency flies may show rescue under hypoxia condition because of decreased oxidative stress. These results suggest PINK1 and Parkin gene as well as CHCHD2 knock out are major causes of mitochondrial dysfunction to lead young onset Parkinson's disease.

P 011

**SNCA G51D missense mutation causing juvenile onset Parkinson's disease**

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**Objectives:** To report the clinical and genetic features in a Parkinson's patient with the SNCA G51D missense mutation.

**Background:**  $\alpha$ -synuclein (SNCA) gene mutations are recognized for causing rare familial forms of Parkinson's disease (PD). The SNCA G51D missense mutation has been associated with a unique parkinsonian phenotype, often overlapping PD and multiple system atrophy, and with abundant pathological accumulation of  $\alpha$ -synuclein. In the few published cases available, symptomatology of G51D patients reveals early onset, levodopa-responsive parkinsonism, pyramidal signs, cognitive impairment, visual hallucinations, and autonomic dysfunction.

**Methods:** Our case is a 23 year-old male of European ancestry with a 9-year history of parkinsonism. He first developed visual hallucinations at age 10, followed by behavioral changes at age 12, and tremors in his left leg and right arm at age 14. He developed profound motor parkinsonism with rapid progression and marked wearing off, dyskinesias, stiffness, and freezing (video). He is responsive to medications including carbidopa/levodopa, rotigotine, and apomorphine, but multiple other PD-medications provided only short-term benefit. Visual hallucinations have been absent in his adulthood. Current neuropsychological evaluation reveals a MMSE 26/30 and intact cognitive function. DBS evaluation is presently underway. Of note, his father died at the age of 42 after having parkinsonism and dementia for about 5 years; autopsy revealed diffuse Lewy Body disease with severe involvement of hippocampal CA2-4 fields.

**Results:** We identified a pathogenic mutation in the SNCA gene, c.152G>A (p.Gly51Asp).

**Conclusions:** This report illustrates a case of the SNCA G51D missense mutation causing parkinsonism with marked motor fluctuations, modest dopaminergic response, and intact cognitive and autonomic function. To our knowledge, our case is the youngest reported for age of onset. While cases in the literature share the G51D genotype, clinical phenotypes remain heterogeneous. Future reports on responsiveness to DBS will be informative regarding therapies and outcomes.

P 015

## The role of environmental toxins (rotenone) in Parkinson's disease

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**Relevance:** Rotenone is a powerful pesticide. It is also a lipophilic compound that easily penetrates the blood-brain barrier. Chronic exposure to low doses of rotenone leads to uniform inhibition throughout the rat's brain. Despite the diffuse effect, rotenone causes selective degeneration of the nigrostriatal dopaminergic pathway, selective oxidative damage to the striatum, and the formation of ubiquitin and  $\alpha$ -synuclein-positive inclusions in nigral cells that are similar to Lewy bodies in Parkinson's disease.

**Materials and methods:** To obtain a rotenone-induced model of Parkinson's disease, the pesticide was administered to rats daily for 4 weeks. The work was performed on male Wistar rats weighing 250-300g. Rotenone was administered subcutaneously at a dose of 2.5 mg / kg.

**Results:** When modeling was observed increased mortality of animals. At the same time, animals showed all the above-described manifestations of Parkinson syndrome. A significant decrease in motor activity occurred within 1 week after the start of the administration of rotenone.

**Conclusions:** The advantages of the rotenone-induced model include the formation of neuronal inclusions and the oxidative stress observed. The main disadvantage of this model is its variability, i.e. lack of behavioral disorders in some animals. In addition, prolonged chronic administration of rotenone leads to a large percentage of experimental rat mortality.

P 016

## Crocus sativus restores damages and oxidative stress induced by lead in meriones shawi: A possible link with Parkinson's disease

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Pb-exposure can cause structural and functional disruption of the NS. Studies have shown that Pb-exposure could be a risk factor in the development of Parkinson's disease (PD). The latter is related to dopaminergic deficiency that may be triggered by genetic and environmental factors such as Pb intoxication.

Our study will focus on the negative effects of oxidative stress on the brain of *meriones shawi*, since it is the organ most exposed to the oxidation due to the high phospholipid content of neuronal membranes and the link existing with the development of neurodegenerative pathologies such as PD. Also, we have evaluated, in one hand, the neurotoxic effect of Pb (25 mg / kg B.W i.p) for three consecutive days on dopaminergic system and locomotor performance in *Merione shawi*. In the other hand, the possible antioxidant effect and restorative potential of *C. sativus* (CS) (50 mg / kg BW) by oral gavage. The immunohistochemical approach has revealed that Pb-intoxicated *Meriones* show a significant increase of Tyrosine Hydroxylase (TH) levels within the Substantia Nigra compacta (SNc), Ventral Tegmental Area (VTA), Locus Coeruleus (LC).

leus (LC), Dorsal Striatum (DS) and Medial Forebrain Bundle (MFB), unlike the control meriones, a group intoxicated and treated with *Crocus sativus* hydroethanolic extract (CSHEE) and treated group by CSHEE. Treatment with CSHEE, has shown a real potential to prevent all Pb-induced damages. In fact, restores the TH levels in SNC, VTA, LC, DS and MFB respectively, similarly, locomotor activity dysfunction in Pb-intoxicated *meriones* was reinstated. In this study, we have revealed a new pharmacological potential of *Crocus sativus* that can be used as a neuroprotective product for neurodegenerative disorders, especially, which implying dopaminergic and noradrenergic injuries, like PD, trigged by heavy metals.

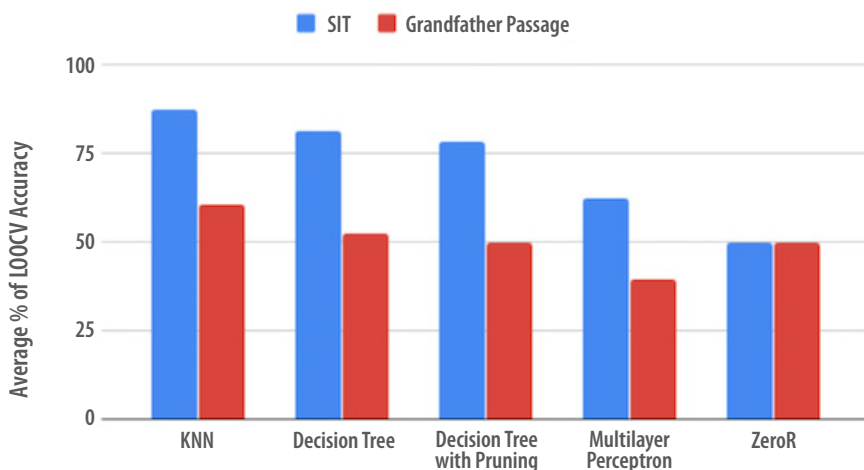
P 017

## The promise of automation: Development and preliminary testing of a language-based machine learning algorithm in PD

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**Objectives:** The use of automated analysis approaches in the clinical diagnosis of PD, and other neurodegenerative disorders, is appealing because it is fast, inexpensive, scalable, and requires minimal setup (Tröger et al, 2017). Machine learning approaches for discriminating PD speakers largely use motor features (Nilashi et al, 2018). Extant research suggests that cognitive declines manifest as speech and language errors in spontaneous production tasks (Burke, 2002). Consequently, algorithms based purely on motor features may have limited clinical utility for detecting cognitive impairment in PD. The proposed work seeks to expand current machine learning algorithms in PD using both motor and language features to discriminate affected speakers from healthy controls.



[Prediction Accuracies of All Models For SIT and Grandfather Passage]



**Methods:** We used language production errors and pausing to classify standardized reading passages (Grandfather Passage) and phonetically balanced sentence sets produced by individuals with PD (n=35 language samples) and healthy controls (n=35). Language samples were manually annotated (in CHAT/CLAN) for word retrieval, morphology, and sound production errors. We included select language production markers shown previously to reflect cognitive impairment in PD (Roberts & Orange, 2013). Manually coded language data were used to train classifiers based on K-Nearest Neighbor, ZeroR, decision tree, and multilayer perceptron approaches.

**Results:** The K-Nearest Neighbor approach applied to a phonetically balanced set of 11 standardized sentences produced the most robust solution correctly classifying 87.5% of the sentence samples and 60.53% of the standardized reading passage samples.

**Conclusions:** Acceptable classification of PD speakers was achieved using a language-feature based machine learning algorithm. While the work requires replication using larger samples, it is a promising first step for a machine learning algorithm sensitive to potential language markers of cognitive decline in PD. Such language-based algorithms can be important tools for remote monitoring of speech cognitive changes in PD.

P 018

## **Low doses of natural pigments improve the motor deficits, the total and mean lifespan of *Drosophila melanogaster* exposed to Parkinson's toxin Rotenone**

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**Objectives:** To test the protective effects of pigments (anthocyanins) from petals of Rosa, Barleria and fruit rind of Garcinia on the natural ageing as well as against Rotenone-induced Parkinsonism and lifespan.

**Methods:** Male *Drosophila* flies (2day old, 100 flies/ group) were treated with plant pigments individually (0.01%, in diet, 2ml/ tube). The flies were introduced to the fresh batch of medium every 4th day. These flies were co-exposed to Rotenone (0.05mM in medium). Mortality was recorded daily and behavioural manifestations were documented weekly.

**Results:** Flies exposed to only plant pigments behaved as that of control flies in climbing and stress assays. They also demonstrated extended total and mean lifespan (24% more) in comparison to control flies. Interestingly, the reduction of lifespan among the flies exposed to Rotenone was partially protected by plant pigments.

**Conclusions:** Our data is a preliminary finding about the lifespan extending activity of the plant pigments per se and against Rotenone induced Parkinson's pathology. However, we have planned detailed experiments to assess the pathophysiology on the specific neurons.

P 022

**Reserpine model of Parkinsonian syndrome**D. Tursunov<sup>1</sup><sup>1</sup>*Tashkent Medical Academy, Medical Biochemistry, Tashkent, Uzbekistan*

**Relevance:** Currently, several experimental models of Parkinson's disease are known: reserpine, methamphetamine, 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine - substances that selectively destroy catecholaminergic systems or disrupt their normal functioning. It has also been found that some agricultural chemicals, such as rotenone and paraquat, when administered systematically, can reproduce a number of key features of Parkinson's disease in rodents.

The reserpine model of Parkinson syndrome was achieved with a single injection of reserpine at a dose of 3 mg / kg subcutaneously. The work was carried out on male Wistar rats weighing 250-300 g. Reserpine was dissolved in glacial acetic acid (100 µl), then in water for injection at a ratio of 1: 35.

**Results:** After the introduction of the toxin, the animals developed the following symptoms: rigidity, ptosis of the upper eyelid and tremor. Reserpine is a central sympatholytic, systemic administration of the drug depletes dopamine in the nerve endings and induces a hypokinetic state in rodents. Reserpine causes the release of other neurotransmitters that may not be directly involved in the molecular pathogenesis of Parkinson's disease.

**Conclusions:** Such model is optimal for studying the possibilities of correcting the pathology with the help of various pharmacological agents. Its advantage lies in the rapid development of Parkinson syndrome in experimental animals: the symptoms occur as early as 2 hours after the administration of the reserve and persist for up to 4 days. On this model, it is possible to study new drug anti-parkinsonian substances with their both systemic and intracerebral administration. The predictive value of testing for symptomatic drugs on the reserpine-induced model is low, since some drugs that reduce reserpine motor impairment are ineffective in Parkinson's disease. However, such a model opens up opportunities for the creation and testing of new drug approaches aimed at reducing the cognitive deficit in Parkinson's disease.

P 024

**Sustained release triple drug loaded colloidosomes for management of Parkinson's disease**S. Bhargava<sup>1</sup><sup>1</sup>*Himalayan University, Kanpur, India*

Parkinson's disease (PD) is well-known as a progressive and degenerative disease of the nervous system. The degeneration of dopaminergic neurons in the substantia nigra, and a reduction in the amount of the neurotransmitter dopamine available in the striatum relate symptoms of this disease. It is hypothesized that a drug delivery system that provides controlled and sustained release of PD drugs would afford better management of PD. Hollow microcapsules composed of PMMA (polymethyl methacrylate) and poly (caprolactone) (PCL) are prepared through a modified double-emulsion technique. They are loaded with three PD drugs, i.e., levodopa (LD), carbidopa (CD), and entacapone (ENT), at a ratio of 4:1:8.

Microcapsules were prepared through a double emulsion (W1/O/W2) solvent evaporation method with modifications to produce hollow microspheres. Microcapsules were then spray coated along with ENT. The microcapsules were analyzed for size distribution and zeta potential using Zetasizer. Shape and surface morphology were studied using SEM. Transmission electron microscope (TEM) was used as a visualizing aid for particle morphology. The average particle size and polydispersity index were determined by optical microscopy using a calibrated oculometer, drug entrapment, CLSM, Buoyancy tests and in-vitro drug release was studied.

LD and CD are localized in both the hollow cavity and PMMA/PCL shell, while ENT is localized in the PMMA/PCL shell. Release kinetics of hydrophobic ENT is observed to be relatively slow as compared to the other hydrophilic drugs. It is further hypothesized that encapsulating ENT into PCL as a surface coating onto these microcapsules can aid in accelerating its release. Now, these spray-coated hollow microcapsules exhibit similar release kinetics, according to Higuchi's rate, for all three drugs.

The results suggest that multiple drug encapsulation of LD, CD, and ENT in gastric floating microcapsules could be further developed for *in-vivo* evaluation for the management of PD.

**P 025**

## **The diabetes drug metformin reverses cognitive impairment and membrane functions in diabetic aging female rat brain: A link with diabetes and Alzheimer's disease**

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**Objectives:** The emerging view is that diabetic brain features many symptoms that are best described as accelerated brain aging. The objective of this study was to investigate effects of metformin on body weight, blood glucose levels, glucose transporter (GLUT1), interleukin 1  $\beta$  (IL-1 $\beta$ ) and protein kinase B expression, antioxidant enzymes levels, expression of synaptic molecules synaptophysin and synapsin I, biomarkers of oxidative stress, lipid peroxidation, membrane fluidity, reactive nitrogen species (RNS) and acetylcholinesterase (AChE) in diabetic aging brain of female rats.

**Methods:** Male Wistar rats, young (3 months) adult (12 months) and aged (24 months) were diabetic by using alloxan monohydrate. Metformin was administered i.p. at a dose of 200mg/kg/day for 30 days to both control and diabetic aging rats. A detailed study was carried on expression of inflammatory cytokines, insulin receptor pathology and synapse, GLUT 1, biomarkers of oxidative stress and AChE activity. Morris water maze with expression of synaptic molecules synaptophysin and synapsin I and ultrastructural studies of brain region by magnetic resonance imaging.

**Results:** Present study shows that there was a similar pattern of increased expression of interleukin, protein kinase B, lipid peroxidation, blood glucose, insulin receptor expression and RNS levels with AChE activity, and a decrease in membrane fluidity, antioxidant enzymes activity and (GLUT1) expression in brain of both aging and diabetes.

On the other hand, metformin treated groups exhibited significant reduction in helped to reverse the age related changes studied, to normal levels. Metformin treatments improved attention and memory

functions with enhanced the levels of synaptic molecules synaptophysin and synapsin I. Our data showed that exogenous administration of metformin brought these changes to near normalcy in diabetic aging female rats.

**Conclusions:** The results illuminate mechanisms of neuroprotection by metformin, and applying new strategies for control of neurodegenerative diseases including metabolic syndrome and Alzheimer's disease.

P 026

## High serum total cholesterol level decreases the risk of Parkinson's disease: A systematic review and meta-analysis

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**Background:** Parkinson's disease is a neurodegenerative disorder, which leads to progressive deterioration of motor function due to loss of dopaminergic neurons in the substantia nigra of the basal ganglia. The disease pathophysiology is largely idiopathic and may result from a complicated interplay of genetic and environmental factors. Recently, a growing number of literature have provided evidence that circulating cholesterol is related to Parkinson's disease. However, these studies have revealed conflicting results with no clear conclusions.

**Methods:** We searched multiple electronic bibliographic databases to identify studies published from 1990 to 2018. Following the application of inclusion and exclusion criteria, the relative risk estimates of all the included studies were employed to estimate the pooled RR using the inverse variance random-effects method.

**Results:** Our study included a total of 266,677 subjects with 7,057 PD cases. High serum cholesterol level was associated with a significantly reduced risk of PD (RR=0.66, 95% CI: 0.52-0.85,  $P < 0.0001$ ). Study result was stable even after sensitivity analysis. There was no evidence of publication bias.

**Conclusions:** In conclusion, our meta-analysis supported the hypothesis that high serum cholesterol was associated with significantly reduced risk of PD. Our findings provide important insights into the molecular pathways underlying the etiology of idiopathic Parkinson's disease and highlight a key role of serum cholesterol level in Parkinson's disease pathogenesis.

P 027

## Genetic analysis of DNA methylation genes in Parkinson's disease

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**Objectives:** To investigate the relationship between the DNA methylation related genes and Parkinson's disease (PD), we conducted a case-control study in a Chinese population.

**Methods:** Using gene-targeted sequencing based on molecular inversion probes (MIPs), 12 genes related to DNA methylation (*DNMT1*, *DNMT3A*, *DNMT3B*, *MBD1*, *MBD2*, *MBD3*, *MBD4*, *MECP2*, *TET1*, *TET2*, *TET3* and *UHRF1*) were sequenced in 1692 sporadic PD patients and 1419 neurologically normal controls of Chinese origin. All of the pathogenic variants were validated by Sanger sequencing. Gene-based association test and burden test were employed to assess the correlation.

**Results:** PD patients (mean age at onset, 48.69±12.33; males, n=922, 54.49%) and controls (mean age, 48.54±16.30; males, n=724, 51.02%) were well matched for age and gender. Common variants rs72799516 in *TET1* and rs111678678 in *TET2* were proved to be associated with PD risk (OR = 0.6464, p=0.02041 for analyses using the allelic model and p=0.02015 for logistic regression analyses (sex + age as covariates); OR = 0.607, p=0.01439 for analyses using the allelic model and p=0.022 for logistic regression analyses (sex + age as covariates)). In the eQTL analysis from GTEx database, we found that rs72799516 in *TET1* can affect *TET1* gene expression in the caudate (basal ganglia) of the brain (p=0.0079). In Braineac database, we showed that rs72799516 in *TET1* can affect the gene expression of *TET1* (p=1.1e-02 (hippocampus) and 1.4e-03 (white matter)), *STOX1* (p=2.0e-02 (cerebellum) and 2.2e-04 (medulla)), *DNA2* (p=2.9e-04 (temporal cortex)), *MYPN* (p=8.5e-04 (thalamus), 2.3e-03 (occipital cortex), and 9.0e-04 (white matter)), *CTNNA3* (p=1.5e-03 (temporal cortex)) and *CCAR1* (p=4.2e-02 (frontal cortex)). Moreover, we identified seven loss-of-function rare variants in *TET2* and multiple predicted pathogenic mutations in *TET* family genes. However, these rare variants were not associated with PD risk.

**Conclusions:** Our study suggested rs72799516 in *TET1* and rs111678678 in *TET2* played a role in the Chinese sporadic PD cohort.

P 028

## Protective effect of antidepressants against rotenone induced Parkinson's like symptoms in Wistar rats

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Parkinson's disease is a second most common age-related neurodegenerative disorder characterized by significant loss of DA neurons of SNpc region of the midbrain. Neurotransmitter alteration is well established to be involved in pathogenesis of PD. The neuroprotective efficacy of antidepressants is well explored in various CNS disorders. The present study was undertaken to identify the possible protective role of different antidepressants (venlafaxine and sertraline) against rotenone induced Parkinsonism like symptoms in rats.

Rats were administrated with rotenone (1.5 mg/kg/day; s.c.) daily for a period of 4 weeks. Venlafaxine (10 and 20 mg/kg; p.o.), sertraline (10 and 20 mg/kg; p.o.) and Levodopa combination with Carbidopa (10 mg/kg; p.o.) were administered daily starting from 7th day one hour prior to rotenone administration. Behavioral parameters were assessed on weekly basis. On 28th day, animals were sacrificed and striatum were isolated for biochemical (LPO, GSH and nitrite), neuroinflammatory (TNF, IL-1 and IL-6), neurochemical (DA, NE, 5-HT, GABA, Glutamate, DOPAC, HVA and 5-HIAA) and mitochondrial complex-I estimation. Rotenone administration significantly altered body weight, motor coordination, oxidative defense, increased pro-inflammatory mediators and decreased level of catecholamines. Pre-treatment with venlafaxine and sertraline significantly attenuated the alteration in behavioral, oxidative stress, neuroinflammation, mitochondrial and catecholamines level in striatum. The study provides evidence that antidepressants might be used as adjuvant therapy in the management and treatment of PD.

## P 029

### Neuronal and astroglial plasticity in copper-induced Parkinsonism: Neuromodulatory effect of curcumin

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**Objectives:** We aim herein to evaluate the influence of acute Cu-intoxication (10 mg/Kg B.W. i.p) for 3 days, then, subchronic Cu-intoxication (0.125%) for 6 weeks on the dopaminergic, serotonergic and astroglial systems together with behavioral impairments. Then, test the therapeutic efficacy of curcumin (30 mg/kg B.W.).

**Methods:** Adult male rats were injected intraperitoneally with 10 mg/Kg and received orally gave of curcumin (30 mg/kg B.W.) for three consecutive days in acute model. In subchronic model, rats were intoxicated with 0.125 % of Cu in drinking water for six weeks, together with treatment by orally administration of curcumin (30 mg/kg B.W.). Locomotor behavior was assessed using the open field, anxiety state was assessed by elevated plus maze and memory function was evaluated by mean of Morris maze test, then, rats were scarified for an immunohistochemical analysis of Tyrosine hydroxylase (TH), serotonin (5-HT), and GFAP.

**Results:** In Cu-exposed rats, we noted a significant increased innervation of 5HT in dorsal raphe nucleus (DRN) and Basolateral Amygdala (BLA) outputs; decreased innervation of TH within Substantia nigra (SNc), Ventral Tegmental Area (VTA), and in striatum dorsal. This was correlated with decreased astroglial plasticity in striatum, DRN, SNc and VTA. Such effects were associated with decreased locomotor performance and anxiogenic-like effects but did not alter learning and memory; Curcumin co-treatment prevented Cu-induced behavioral impairments and reversed 5-HT, TH and astroglial alterations and main spatial learning and memory performance was remarked in treated rats with curcumin in Morris water maze

**Conclusions:** These results demonstrated that Cu intoxication induced an evident impaired neuroplasticity that was alleviated with curcumin treatment. Therefore, curcumin may be valuable in the treatment of metals-induced neurobehavioral deficits. The impairment of monoamine neurotransmitters may be one of the major mechanism implicated.

P 030

## **Altered nigrostriatal dopaminergic innervation in rat model of acute liver: A possible cause of parkinsonism in hepatic encephalopathy**

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**Objectives:** Hepatic encephalopathy (HE) is a progressive neuropsychiatric disorder that manifests itself in both acute and chronic liver failure. The presence of extrapyramidal symptoms, including rigidity and tremors, may reflect alterations of several neurotransmitters, including dopamine, GABA, glutamate or serotonin. The present study aimed to evaluate dopaminergic, serotonergic, and possible correlations with locomotor activity in an animal model of acute hepatic encephalopathy in rats.

**Methods:** Induction of acute hepatic insufficiency was achieved in rats by repeated i.p administrations of thioacetamide (TAA) (300 mg / kg), 1 injection / day for 3 consecutive days. While the controls received a physiological saline buffer (0.9% NaCl). Using immunohistochemistry and the open-field assay, we evaluated respectively the expression of tyrosine hydroxylase (TH) in the substantia nigra and serotonin level in the nucleus and the locomotor activity of dorsal Raphe 12 hours after TAA rats compared with the witnesses.

**Results:** our results showed a significant decrease in the level of TH in the substantia nigra and a loss of serotonin immunoreactivity in the dorsal Raphe nucleus, and this was concomitant with hypoactivity in TAA rats compared to controls.

**Conclusions:** the present study seems to imply the loss of innervations of dopamine in the brain as well as serotonin as the possible neuronal basis of hypolocomotion, known to occur in acute hepatic encephalopathy.

P 031

## **SLC6A4 - A 44-bp insertion/deletion association with Parkinson's disease in South Indian population**

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Parkinson's Disease (PD) is second most common neurodegenerative, slow progressive disease. degeneration of dopaminergic neurons leading to depletion of Dopamine (DA) in substantianigra pars compacta (SnPc) leading to motor and non motor complications in PD. Age, genetic and environmental factors play important role in pathogenesis of PD. The 5-HTT gene (SLC6A4) contains a 44-bp Insertion/deletion in promoter region.

The insertion/ deletion in the promoter region appear to be associated with PD risk in different ethnic populations.

**Objectives:** To investigate the association of 44bp insertion/deletion of SLC6A4 gene with PD in south Indian PD patients.

**Methodology:** A total of 125 PD patients and 107 age and ethnicity matched healthy controls were included in the study. Genomic DNA was isolated using phenol-chloroform protocol. Polymerase Chain Reaction (PCR) was carried out to amplify the target DNA and the restriction fragment length polymorphism (RFLP) technique was used for identification of polymorphisms. Sanger's sequencing method was performed for validation of identified polymorphisms.

**Results:** The results from this study demonstrate that SLC6A4 44bp insertion/deletion polymorphism showed significant association with PD (OR: 0.29, 95% CI: 0.13-0.65,  $p=0.002$ ).

**Conclusions:** Our study suggests that significant association of SLC6A4 Gene Polymorphisms in the risk of PD in south Indian patients.



## Topic: Parkinson's disease - Imaging and biomarkers

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P 032

### Correlation between peripheral immunological characteristics and clinical phenotypes in patients with Parkinson's disease

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**Objectives:** To analyze the peripheral blood immunological characteristics of patients with Parkinson's disease (PD) and to explore their correlation with patients' clinical symptoms.

**Methods:** According to the 2015 MDS PD diagnostic criteria, PD patients who were admitted to the outpatient department of the Tongji Hospital of Tongji University from June 2018 to December 2018 were enrolled. And the healthy control group with similar demographic characteristics was recruited. Peripheral blood of all enrollees was collected and the proportion of immune cells subsets were analyzed by flow cytometry analysis. The clinical symptoms of PD patients were evaluated by the relevant scales. All statistical tests were conducted with SPSS version 20.0 statistical software. P-value < 0.05 considered as statistically significant.

**Results:** A total of 43 PD patients and 38 controls were enrolled. There were no significant differences in gender and age between the two groups. In terms of peripheral blood immune characteristics, the proportion of T lymphocyte subpopulation (%) of CD28+CD27-CD3+CD4+ in the PD group (7.55(5.30, 11.95)) were significantly reduced compared with the control group (9.60 (7.70, 13.95)) (p=0.024), and other peripheral immune cells subsets was not significantly different between the two groups.

There were moderate correlations between PD motor symptoms and the proportion of B cells, T cell subpopulation of CD45RA+CD45RO-CD3+CD4+, CD45RA-CD45RO+CD3+CD4+ and CD28+CD27-CD3+CD4+ (r=-0.423; r=-0.316; r= 0.304; r= 0.369). For non-motor symptoms, constipation was moderately correlated with T cell subpopulation of CD8+CD27+CD3+CD8+ and CD28-CD27-CD3+CD8+ (r=0.343; r=-0.331), and sleep quality and cognitive ability was moderately correlated with T cell subpopulation of CD38+HLA-DR+CD3+CD4+ (r=0.324; r=-0.328).

**Conclusions:** The peripheral blood immunological characteristics of patients with PD were different from those of the control group, and there was a certain correlation between patients' clinical symptoms and their proportion of immune cells subpopulations.

P 035

## Clinico-radiological correlates of impaired cerebral autoregulation in patients with Parkinson's disease

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**Objectives:** To evaluate the clinical and magnetic resonance imaging changes associated with impairment of cerebral vasoreactivity (CVR) in patients with Parkinson's disease (PD).

**Methods:** Patients with idiopathic PD diagnosis<sup>1</sup> underwent transcranial Doppler ultrasound, baseline and after hypercapnic stimulus (7% carbon dioxide 5-minute inhalation). Severity was assessed with Hoehn & Yahr (H&Y), and motor (MDS-UPDRS) scales. CVR was defined as a percentage difference in the mean flow velocity less than 5%<sup>2</sup>. All sonograms were performed in the ON state. Magnetic Resonance white matter changes (leukoaraiosis) were evaluated with Fazekas scale.

**Results:** 72 patients were included. Impaired CVR was found in 39 patients (54.2%), in which a non-tremor dominant phenotype at onset was significantly higher ( $p=0.013$ ), and significantly higher levodopa equivalent and total daily dose ( $p=0.025$  and  $p=0.045$ ), without difference in disease duration, or severity by Hoehn & Yahr or MDS-UPDRS III. Patients with impaired CVR had a significantly higher prevalence of white matter changes ( $p=0.019$ ).

**Conclusions:** In PD patients, impairment of cerebral vasoreactivity is highly prevalent and associated with of white matter changes (but not severity), and higher levodopa doses, albeit unrelated to disease severity or duration.

### References:

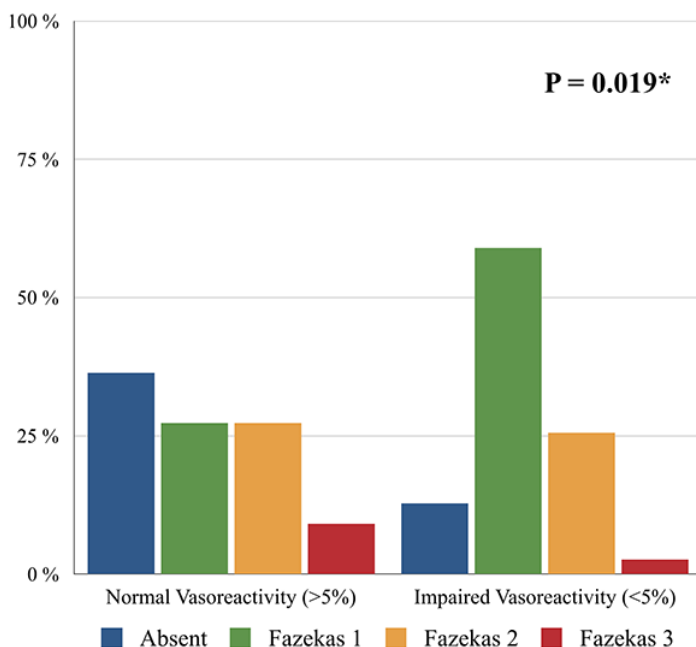
1. Postuma et al (2015). *Mov Disord* 30(12): 1591-1601.
2. Zamani et al. (2011). *Clin Neurol Neurosurg* 113(5): 368-372.

	Normal CVR (>5%) (n= 33)	Impaired CVR (<5%) (n= 39)	P
Disease duration, mean $\pm$ SD	6.7 $\pm$ 5.0	6.2 $\pm$ 4.8	0.695**
NTD subtype at onset, n (%)	9 (27.3)	22 (56.4)	0.013*
Hoehn & Yahr, mean $\pm$ SD	1.8 $\pm$ 1.1	1.9 $\pm$ 1.1	0.734**
LEDD, mean $\pm$ SD	689.3 $\pm$ 383.1	965.9 $\pm$ 610.6	0.025**
MDS-UPDRS III, mean $\pm$ SD	26.9 $\pm$ 20.5	27.1 $\pm$ 20.2	0.961**

CVR, Cerebral Vasoreactivity. NTD, Non-Tremor Dominant. LEDD, Levodopa Equivalent Daily Dose.

\*Mann-Whitney U. \*\*Chi square.

[Comparison of clinical variables]



[Fazekas grade comparison between groups]

**P 036**

## Non-motor burden is associated with the patterns of striatal dopamine loss in de novo Parkinson's disease

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**Objectives:** Ample evidence has suggested that non-motor symptoms (NMS) in Parkinson's disease (PD) are related to deficits in multiple neurotransmitter systems, including dopaminergic system. In this study, we explored whether early NMS burden was associated with different patterns of nigrostriatal dopamine depletion in patients with de novo PD.

**Methods:** We consecutively recruited 255 patients with de novo PD who visited the movement disorders outpatient clinic from October 2016 to December 2018. All patients underwent <sup>18</sup>F-FP-CIT PET scans and the NMS Questionnaire (NMSQuest) to assess the overall NMS burden.

Based on the NMSQuest scores, the patients were divided into the mild level of NMS burden (PDNMS-mild; NMSQuest score < 6 ; n = 91) and severe level of NMS burden groups (PDNMS-severe; NMSQuest score > 9 ; n = 90).

Then, we compared the striatal dopamine transporter (DAT) availability between the groups.

**Results:** Patients in the PDNMS-severe group tended to be older ( $p = 0.073$ ), and had more severe parkinsonian motor signs than those in the PDNMS-mild group despite comparable DAT availability in the posterior putamen. The PDNMS-severe group exhibited more severely decreased DAT availability in the anterior caudate, posterior caudate, anterior putamen, and ventral striatum compared to the PDNMS-mild group. Moreover, the inter-sub-regional ratio of the associative striatum to the sensorimotor striatum was lower in the PDNMS-severe group.

**Conclusions:** The present study demonstrated that PD patients with severe level of NMS burden exhibited relatively diffuse dopamine depletion throughout the striatum. These findings suggest that the overall burden of NMS would be closely linked to dopamine depletion in the striatal sub-regions other than the sensorimotor striatum in de novo PD.

P 038

## Abnormal smooth pursuit in Parkinson's disease: A possible marker of disease progression

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**Objectives:** To determine the prevalence of smooth pursuit eye movement (SPEM) abnormalities in Parkinson's disease (PD).

**Background:** SPEM are conjugate eye movements that track a moving object in order to maintain fixation on the object. Saccadic intrusions (SI), which are an abnormal SPEM, can be thought of as a form of oculomotor bradykinesia. SI are found in PD and separately with healthy aging. The natural history of SI in PD has not previously been presented.

**Design and Methods:** A chart review was performed collecting data on idiopathic PD patients who were treated by a movement disorders neurologist. This neurologist performed oculomotor testing on all patients at all visits. A total of 328 charts from 2013-2018 were reviewed and separated into 3 categories: Those who had never had SI on physical exam (NSI), those who always had SI (ASI), and those who intermittently had SI (ISI). The ISI group was further separated into two groups: those who had SI on the first initial visit, and those who did not.

**Results and discussion:** Of 328 patients, there were 137 with NSI (42%), 27 with ASI (8%), and 164 with ISI (50%). Combining the ASI and ISI, 58% of our PD patients had SI at least once during follow up. Of those with ISI, 132 (80%) had no SI at initial evaluation and developed it later.

The natural history of SI in SPEM in PD is not well documented. Corin (1972) reported 76% of PD patients had some kind of oculomotor abnormality. White et al (1983) found all of their 14 PD patients to have reduced gain in SPEM. We report 58% of PD patients have SI at some point in their disease and that SI are not present in most patients with PD at initial evaluation. SI can be considered an indicator of PD progression.

P 039

## Clinical correlates of hyposmia in a multi ethnic cohort of idiopathic Parkinson's disease

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**Objectives:** To explore clinical and ethnic correlates of hyposmia in idiopathic Parkinson's disease (PD).

**Methods:** A cross-sectional analysis of 173 participants enrolled in the Non-motor Longitudinal International Study (NILS; UKCRN No: 10084) for whom ethnicity (White (W), Black African and Caribbean (BAC), and Asian (A)) was recorded and who also underwent a dopamine transporter scan (DaTscan).

Hyposmia scores on question 28 of the Non-Motor Symptom Scale (NMSS) were used to stratify participants based on hyposmia severity: absent 0 (n= 105; 50 W, 37 BAC, 18 A), mild/moderate 1-7 (n = 41; 28 W, 9 BAC, 4 A), and severe 8-12 points (n= 27; 19 W, 4 BAC, 4 A).

Differences in non-motor and motor scores, and DaTscan results were assessed by Kruskal-Wallis test.

**Results:** No differences were observed for age, disease duration, Levodopa equivalent daily dose across the different groups as defined by item 28 of NMSS ( $p \geq 0.13$ ).

Within the W group we observed significant differences in sleep-fatigue, mood-cognition, attention-memory ( $p \leq 0.008$ ), in the NMSS total score ( $p < 0.001$ ), HADS scores (both anxiety and depression;  $p \leq 0.003$ ).

In the BAC group, we observed no differences in any of the NMS, but there were significant differences for DaTscan outcome measures ( $p \leq 0.019$ ) with most pronounced differences in the bilateral putamen and left striatum.

In the A group, we found no differences in any of the NMS or DaTscan outcome measures.

**Conclusions:** PD patients with hyposmia appeared to have a specific non-motor profile consisting of sleep disturbances, mood and cognitive problems. This was only true in the White population. In the Black African and Caribbean population, on the other hand, hyposmia severity correlated with putaminal dopamine binding ratios. These results underscore the ethnic differences in PD which need to be considered, not only for hyposmia.

P 040

## MRI features study of Parkinson's disease and vascular parkinsonism in Uzbekistan

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**Objectives:** MRI study on Parkinson's disease (PD) has not been studied before in Uzbekistan. We aimed to identify instrumental differential diagnostic criterias for Parkinson's disease and vascular parkinsonism using the MRI method.

**Material and methods:** 26 patients with PD (mean age  $46.2 \pm 2.9$ ) and 20 patients with vascular parkinsonism (mean age  $68.2 \pm 4.2$ ) were referred to the Tashkent Medical Academy in the period 2013-2016. All patients underwent MRI of the brain, analyzed signs of expansion of the ventricular system, expansion of the basal cisternal space, sylvium gaps, severity of the diffuse atrophic process.

**Results:** Structural changes in the medulla ( $p < 0.05$ ) and moderately expressed internal hydrocephalus ( $p < 0.05$ ) were significantly less frequent in patients with BP, whereas lacunar infarctions and moderately expressed leukoareosis occurred only in single cases. In these cases, analysis of the clinical picture of the disease, the nature of the neurological symptoms, the absence of a complex of vascular risk factors allowed talking about BP, but not about the joint venture. Lacunar foci ( $p < 0.05$ ) and expressed leukoareosis ( $p < 0.05$ ) were more often detected in patients with joint ventures, the frequency of their detection correlated with the presence and severity of arterial hypertension ( $r = 0.412$ ,  $p < 0.01$ ). A purposeful study of the anamnestic data did not allow revealing the earlier episodes of acute cerebrovascular accidents, which allowed to identify focal changes identified by MRI as "mute" strokes.

**Conclusions:** In patients with vascular parkinsonism, focal (lacunar) changes in foci and pronounced leukoareosis are significantly more often detected with MRI, their frequency correlates with the severity of arterial hypertension ( $r = 0.412$ ,  $p < 0.01$ ). In patients with PD, focal changes in the brain substance are rarely detected, however, internal hydrocephalus is more often detected.

#### P 041

### Evaluation of genetic influence of MAPT on clinical and motor functions among Idiopathic Parkinson's disease patients: A comparative study

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**Background:** MAPT H1 and its sub haplotype H1c are reported to be associated with increased risk for Parkinson's disease.

**Objectives:** Study the effect of different MAPT haplotypes on clinical and motor functions among Idiopathic Parkinson's Disease (IPD) patients.

**Methods:** This study included 50 patients diagnosed with IPD based on UK Brain Bank criteria; with & without cognitive impairment.

Patients were divided into 2 groups:

Group I: including 12 patients with IPD and H1 homozygous haplotype (H1/H1).

Group II: including 38 patients with IPD and other haplotypes (H1/H2 or H2/H2).

MAPT Genotyping was performed using real-time PCR

**Results:** Although the mean age of patients in Group I was lower than that in Group II (59.6ys & 61.1ys respectively); but no statistical significant difference was detected. Male to female ratio was 5:1 in H1 haplotype patients and 1.7:1 in other haplotypes patients. Fifty percent of the patients were H2/H2 genotype and 24% were H1/H1 genotype. Although the mean age at onset of disease was earlier in Group I patients compared to Group II (56.2ys & 57.5ys respectively); but no statistical difference was detected. The mean duration of illness was lower in Group I patients compared to Group II (3.41ys & 4.02ys respectively); but

no statistical significant difference was detected. Tremor predominant type was more in Group I (83.3%), and more compared to Rigidity predominant type; with no statistical significant difference between both groups. UPDRS-Total was nearly equal in both Groups, with no statistical significant difference detected.

**Discussions:** The MAPT haplotypes contribute to the expression of motor features of PD. The association between the H2 haplotype and global parkinsonism is no longer detected.

**Conclusions:** Apart from association with cognitive decline in PD patients; there was No evidence to support an association between H1 homozygous haplotype patients and severity of motor features.

#### P 043

### MRI cortical layer study in patients with Parkinson's disease in Uzbekistan

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**Objectives:** Cortical layer dedicated study using MRI has not previously studied in Movement disorders in Uzbekistan before. We aimed to establish, using MRI, the presence of differences in the thickness of the cortical layers in patients with early and developed stages of Parkinson's disease (PD).

**Materials and methods:** There were examined 22 PD-patients with stages 2 (group 1) and 3 (group 2) according to the Khen-Yar functional scale, of which 12 patients had an akinetic-rigid form of the disease (54.5%), the remaining patients had mixed form of PD (45.5%).

**Results:** We found significant differences in the thickness of the cortex in both the left and right hemispheres of the brain. One of the most interesting obtained results is the degeneration in the area of the visual cortex. Pathology of the posterior dorsal cingulate gyrus (1 group -2,758; 2 -group - 2,624;  $p = 0.017$ ) affects the performance of episodic memory operations and the ability to understand and be aware of the opinions of other people. There is a decrease in the thickness of the cortical layer (1 group-2.21; 2-group-2.11;  $p = 0.044$ ), which negatively affects cognitive and mental disorders that develop in patients with PD. Changes in the fusiform gyrus (1 group-1.83; 2-group-1.75;  $p = 0.042$ ) have a negative effect primarily on the state of cognitive functions of patients and is one of the mechanisms for the development of hallucinations.

**Conclusions:** The obtained data allow us to establish a connection between the non-motor manifestations of PD and the degeneration of certain cortical regions of the brain. In this regard, it is necessary to further develop and improve high-tech techniques that will contribute to clarifying the issues of pathogenesis and predicting the course of PD.

## P 044

**Deficits in executive function in amnesic mild cognitive impairment: Event-related potentials study during stroop color-word task**L. Gu<sup>1,2</sup><sup>1</sup>Southeast University, Nanjing, China, <sup>2</sup>Southeast University, Affiliated ZhongDa Hospital, Medical School, Nanjing, China

**Background:** Previous investigations showed that Alzheimer's disease (AD)-related executive function deficits start near the beginning of mild cognitive impairment (MCI) phase of itself. The study aimed to explore deficits in executive function in amnesic MCI (aMCI) with Event-Related Potentials (ERPs) study.

**Methods:** The ERP data were measured and analyzed in 30 aMCI and 38 healthy elderly controls (HEC) during Stroop Color-Word Task (SCWT).

**Results:** The study indicated that aMCI patients showed decreased accuracy (ACC) and delayed reaction time (RT) in incongruent condition, compared to HEC (all  $p < 0.05$ ). Additionally, aMCI patients showed greater N450 amplitudes of a difference wave between ERPs elicited by incongruent and congruent stimuli at Fz electrode, compared to HEC (all  $p < 0.05$ ). Moreover, standardized low-resolution brain electromagnetic tomography analysis (sLORETA) study showed a hyperactivation in the left inferior parietal lobule (IPL) in the contrast for the incongruent condition relative to the congruent condition, compared to HEC during N450 time range ( $p < 0.05$ ).

**Conclusions:** The study showed deficits in conflict processing in aMCI with an ERP study. And the deficits might derive from the left IPL. Hence, the study demonstrated that ERP with SCWT was a sensitive biomarker for recognizing aMCI patients from HEC.

## P 045

**Study of interleukin in blood serum patients with Parkinson's disease**D. Azizova<sup>1</sup><sup>1</sup>Tashkent Medical Academy, Tashkent, Uzbekistan

Parkinson's disease (PD) is progressive neurodegenerative disease, the etiology of this disease in most cases remains unknown, but thanks to numerous studies it becomes obvious that neuron death is the result of not only one, but several reasons. Research was to study concentration interleukin proinflammatory cytokines (IL) -1, (IL) -2, (IL) -4, (IL) -6 and TNF alpha in the serum of patients Parkinson's disease and assess its relationship with clinical manifestations of the disease.

**Methods:** 29 patients and 19 people in the control group had determined the concentration of pro-inflammatory cytokines interleukin (IL) -1, (IL) -2, (IL) -4, (IL) -6 and TNF alpha in serum method of solid phase enzyme immunoassay using a set of reagents company "Vector Best".

**Results:** In 37.5% of patients there was an increase indicator IL-1 and 10% increase indicator alpha TNF, indicating a long inflammatory response in the development of the immune response. The concentration of IL-1 in the serum of patients varied from 0 to 150.0 pg / ml. Median IL-1 concentration in patients the main group (75; 5.5-150.0 pg / ml) was significantly higher ( $p = 0.042$ ) than in the control group (5.5; 0.0-11 pg / ml). The concentration of alpha TNF in the serum of patients ranged from 0 to 133.5 pg / ml. Median



concentration TNF alpha in patients of the main group (66; 0-133.5 pg / ml) was significantly higher ( $p = 0.052$ ) than in the control group (4.5; 0.0-6 pg / ml).

**Conclusions:** Patients with Parkinson's disease have significantly higher levels of IL-1 and TNF alpha in serum compared to the control group.

The involvement of inflammation in the pathogenesis and symptom formation Parkinson's disease, especially its non-motor manifestations, suggests the need to research potential therapeutic potential of anti-inflammatory drugs for this disease.

**P 046**

## Preclinical trial of a provocative pharmacological test for diagnosing of Parkinson's disease at the prodromal stage

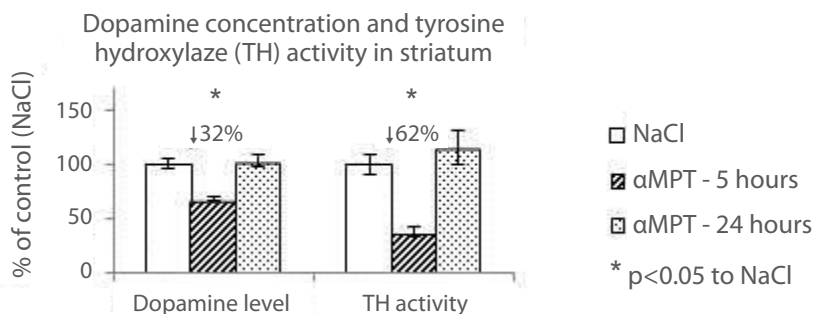
A. Kim<sup>1</sup>, E. Pavlova<sup>1</sup>, A. Kolacheva<sup>1</sup>, L. Dilmukhametova<sup>1</sup>, V. Safandeev<sup>1</sup>, V. Blokhin<sup>1</sup>, M. Ugrumov<sup>1,2</sup>

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**Objectives:** Development of early diagnosis of Parkinson's disease (PD) at the preclinical-prodromal stage is of high priority. This study aimed to develop the provocative test for detection of latent failure of nigrostriatal dopaminergic neurons by intranasal administration of  $\alpha$ -methyl-p-tyrosine ( $\alpha$ MPT), a reversible inhibitor of dopamine synthesis.

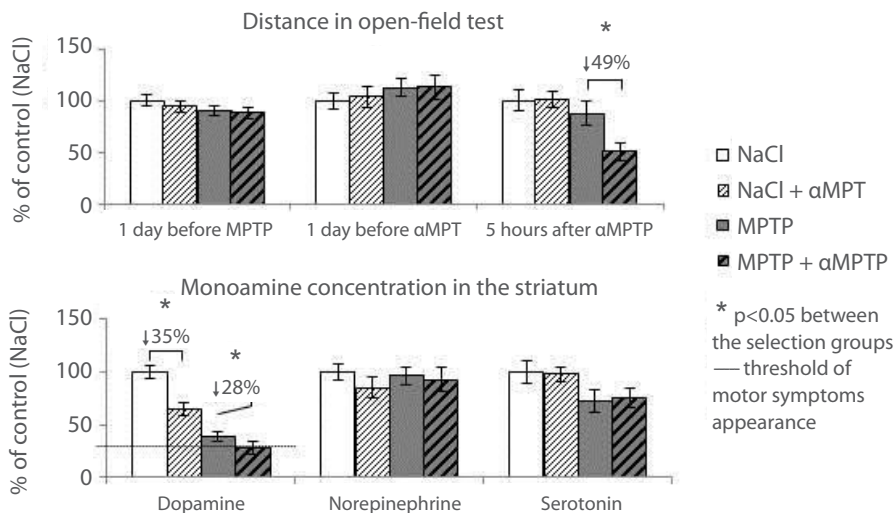
**Methods:**  $\alpha$ MPT was administered intranasally to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice at the presymptomatic stage of parkinsonism or to saline-treated mice (control). Concentration of monoamines in the striatum was assessed by HPLC with electrochemical detection. Tyrosine hydroxylase activity was evaluated by L-DOPA accumulation after inhibition of DOPA decarboxylase with NSD-1015. Pharmacokinetics of  $\alpha$ MPT in plasma and tissues was assessed by HPLC with fluorescence detection. Motor activity of mice was analyzed with open-field test.

**Results:** Maximum decrease of dopamine content in the striatum was observed 5 h after administration of  $\alpha$ MPT, and this period was used for further experiments. Dopamine content and tyrosine hydroxylase activity in the striatum were restored for the next 24 hours.



[Effect of  $\alpha$ MPT on striatal dopamine content and tyrosine hydroxylase activity of intact mice]

As follows from the assessment of pharmacokinetics, three times more  $\alpha$ MPT is delivered to the brain after intranasal administration, than after intravenous administration of the same dose. In turn, the plasma  $\alpha$ MPT concentration was 10 times lower after intranasal administration than after intravenous injection of this inhibitor, what could help to avoid peripheral side-effects. In mice on the presymptomatic model of PD, but not in control, administration of  $\alpha$ MPT provoked the appearance of motor disorders due to threshold decrease of striatal dopamine.



*[Motor activity and monoamine content in the striatum of control and MPTP treated mice after administration of  $\alpha$ MPT]*

**Conclusions:** We have developed and preclinically validated a novel technology for early diagnosis of PD, based on provocative test.

## Topic: Parkinson's disease: Clinical science, therapeutics, surgical management

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P 047

### Efficacy of CVT-301 (levodopa inhalation powder) for treatment of OFF periods in Parkinson's disease

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**Objectives:** Inbrija (CVT-301) is a levodopa inhalation powder developed for the intermittent treatment of OFF episodes in patients on a carbidopa/levodopa regimen. In the phase 3, SPAN-PD<sup>SM</sup> study CVT-301 84mg significantly improved motor function, measured by improvement in Unified Parkinson's Disease Rating Scale motor score (UPDRS-III) score 30 minutes postdose at 12 weeks. In addition, 57.7% on CVT-301 84mg turned ON within 60 minutes compared with 36.1% on placebo. A post-hoc analysis of Parkinson's disease patients achieving  $\geq 30\%$  reduction in UPDRS-III over the first hour of treatment with placebo or CVT-301 was performed. Reduction of  $\geq 30\%$  in UPDRS-III has been used as a marker of improvement in response to levodopa.

**Methods:** UPDRS-III score was measured for 60 minutes postdose with CVT-301 60mg and 84mg vs placebo. Post-hoc analysis evaluated percentage of patients with  $\geq 30\%$  reduction in UPDRS-III score pre- to postdose within the first hour. The proportion of patients in the CVT-301 60-mg and 84-mg groups who achieved  $\geq 30\%$  reduction in UPDRS-III score at each of the time points, and the average across all time points, were compared to placebo.

**Results:** At 12 weeks a greater percentage of CVT-301 treated patients achieved a  $\geq 30\%$  reduction in UPDRS-III compared to placebo at 30 minutes (52% for CVT-301 84mg,  $P=0.02$ ; 53% for 60mg,  $P=0.01$ ; 35% for placebo). At 10 minutes, percentages were: 27% for the 84-mg group ( $P=0.02$ ), 24% for 60-mg group ( $P=0.08$ ), and 14% for the placebo group. Averaged across all timepoints, percentage of CVT-301 treated patients with  $\geq 30\%$  UPDRS-III reduction was greater than placebo (45% for both CVT-301 84mg ( $P=0.02$ ) and 60mg ( $P=0.02$ ); 29% for placebo).

**Conclusions:** More CVT-301 treated patients had clinically-relevant improvements in their motor function by achieving  $\geq 30\%$  reduction in UPDRS-III compared to placebo. These observations support the efficacy of CVT-301 in the treatment of OFF periods.

P 048

## STN LFP and SUA characterization of dyskinesia in PD using microelectrode recordings

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**Objectives:** To describe the single unit activity (SUA) and local field potential (LFP) characteristics of a patient with idiopathic Parkinson's disease (PD) during a dyskinesia episode.

**Methods:** We describe a case report of an individual undergoing bilateral subthalamic nucleus (STN) DBS for treatment of motor complications associated with PD. Intraoperative left hemispheric microelectrode recordings (NeuroProbe, AlphaOmega) of SUA and LFP were made simultaneously approximately 2.5 hours after the last known levodopa intake. Recordings started from 10mm above and extended to 5mm below the dorsal border of the STN. During the recordings, the patient exhibited generalized dyskinesia.

**Results:** Of 14 neurons isolated, almost all showed tonic firing (fast and some irregular) with a mean firing rate of  $63.0 \pm 29.8$  Hz, (higher than previously reported in the unmedicated state). No neurons showed bursting activity as quantified with ISI histograms showing single peaks. LFP activity was characterized by weak beta (22Hz) oscillations, a sharp gamma (80Hz) peak, and strong high frequency oscillations (HFOs) around 300Hz. No coupling between beta and HFO was seen, as previously reported in medicated patients. The SUA was not phase coupled to beta LFP (unlike previously described unmedicated PD patients). Interestingly, sharp gamma activity commenced 10mm above the STN, indicating broader network synchronization. Contralateral dyskinesia improved during stimulation testing of the DBS lead.

**Conclusions:** This case demonstrates unique SUA and LFP findings during a dyskinesia episode in PD, highlighting the need for a more complete understanding of local and network dynamics in PD for use in closed loop DBS systems.

P 049

## Structured clinical documentation to improve quality and support practice-based research in Parkinson's disease

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**Objectives:** To develop and use standardized structured clinical documentation support tools within the electronic medical record (EMR) to improve quality of care and facilitate practice-based research.

**Methods:** We developed a standardized structured clinical documentation support toolkit (SCDS) specific to Parkinson's disease (PD) in the EMR. The toolkit content was developed to conform to Best Practices with physician consensus. The toolkit assigns tasks to care team members and captures hundreds of fields

of discrete data that write to the office visit note. The toolkit includes relevant score test measures, autoscores, and provides interpretation of these scores. We have incorporated Best Practice Advisories (BPA) to alert physicians at the point-of-care when quality improvement options exist. In addition, if the patient meets inclusion criteria, the toolkit prompts enrollment in our DNA bio-banking study.

**Results:** As of January 1, 2019, we have evaluated 3998 patients at initial visit using the PD toolkit. Of these, 778 fulfilled the Bower criteria for definite PD and 320 for probable PD. We present descriptive characteristics of our PD cohort as well as screenshots of our toolkits and BPAs. We continue to follow our patients using the toolkit longitudinally at annual intervals and have enrolled 619 patients in our DNA bio-banking study for genotype analysis to date.

**Conclusions:** The EMR can be standardized to support Best Practices and conduct practice-based research. We are currently sharing our toolkits with other PD clinics as part of the Neurology Practice Based Research Network to promote data sharing and conduct quality improvement research. Importantly, the longitudinally captured discrete data from multiple and diverse PD cohorts can help better characterize the disease phenotype and course, allow for genotype-phenotype correlations, and the development of predictive models.

P 050

## **NILO-PD: A phase 2A study of nilotinib in patients with advanced Parkinson's disease: Study design and status update**

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**Objectives:** To assess the safety and tolerability of nilotinib (150-300 mg once daily) in moderate/advanced Parkinson's disease (PD). Nilotinib is FDA approved for chronic myeloid leukemia but not for PD. Several cell and animal model studies suggest that nilotinib, a c-ABL inhibitor FDA approved for certain types of leukemia, reduces alpha-synuclein pathology in PD, suggesting its potential as a disease-modifying therapy. In addition, a small open-label clinical study in PD reported positive, though exploratory, signs of clinical benefits.

**Methods:** NILO-PD is a Phase 2a randomized, double-blind, placebo-controlled, parallel group study. The study enrolled 76 participants with moderate to advanced PD. Participants were randomized 1:1:1 to nilotinib once per day (150 mg: 300 mg) or placebo for 6 months. The primary outcome is safety and tolerability.

Secondary and exploratory outcomes include assessment of symptomatic effects of nilotinib, impact of nilotinib on progression of PD disability (MDS-UPDRS OFF/ON), cognitive function (DRS-2), quality of life, pharmacokinetics, and a battery of serum and spinal fluid biomarkers.

**Results:** The study is conducted at 25 Parkinson Study Group (PSG) sites in US. Recruitment started in November 2017 and was completed in December 2018. 125 participants were screened and 76 randomized (39.2% screen failure). Baseline characteristics of study participants are summarized by mean (standard deviation): 64.6 (7.5) years of age, 31.6% female, 54.7 (8.0) years at diagnosis, 9.9 (4.7) years disease duration, 66.4 (19.5) MDS-UPDRS OFF score, 48.3 (16.1) MDS-UPDRS ON score, 27.1 (2.2) MOCA score. The study is scheduled to complete subjects' ascertainment in September 2019 and primary outcome results are expected by December 2019.

**Conclusions:** This study will provide further information on safety/tolerability, dose selection and biomarkers of nilotinib as a potential novel symptomatic and disease-modifying therapy for PD, and determine if it is warranted to proceed with future studies in PD de novo population.

## P 051

### Insomnia subtypes and manifestations of prodromal neurodegeneration: A nation-wide population-based study in the Canadian longitudinal study on aging

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**Objectives:** To identify the association between isolated sleep-onset/maintenance insomnia and signs of prodromal neurodegeneration in the 30,097-person Canadian Longitudinal Study on Aging Cohort, aged 45-85.

**Methods:** Isolated sleep-onset and maintenance insomnia symptoms were assessed using questions adapted from the Insomnia Severity Index. Participants who endorsed either (but not both) of the onset and maintenance insomnia questions at least 3 times per week were included in this analysis. Participants self-reporting dementia/parkinsonism were excluded. The primary analysis compared those with isolated symptom of sleep-onset/sleep-maintenance insomnia. A comprehensive list of prodromal neurodegenerative signs/symptoms and objective assessments were analysed cross-sectionally, adjusting for age and sex, via logistic regression.

**Results:** Overall, 2,112 screened positive for onset insomnia alone and 4,465 for maintenance insomnia alone, while 2,504, excluded from this analysis, endorsed both subtypes. Women were more likely to endorse either insomnia subtypes than men (onset OR=1.81, 95%CI=[1.65,1.98]; maintenance OR=1.21[1.13,1.29]). Onset insomnia participants had less education (OR=0.94[0.92,0.96]) and lower income (OR=0.99[0.99,0.99]) than the maintenance insomnia group, which was no different from those with

no insomnia. Participants with onset insomnia had poorer balance (OR=1.27[1.08,1.49], slower gait-speed (OR=1.54[1.32,1.78]) and more motor symptoms (OR=1.66[1.35, 2.04]) than those with maintenance insomnia. Relative to the maintenance insomnia group, onset insomnia participants performed poorer on cognitive tasks (F-A-S test: OR=1.35[1.15,1.53]; immediate recall: OR=1.28[1.12,1.46]); delayed recall: OR=1.22[1.06,1.39]; Miami Prospective Memory Task: OR=1.31[1.13,1.52]).

Depression/anxiety (OR=1.81[1.61,2.04]) and possible REM sleep behavior disorder (OR=1.33[1.01,1.73]) were positively associated with both insomnia symptoms. Onset insomnia participants also had lower heart-rate-variability comparing to the controls (OR=1.19[1.05,1.35]) and maintenance insomnia (OR=1.21[1.05,1.40]).

On average, those with onset insomnia had more neurodegenerative markers (total-abnormal-signs=1.91 vs. 1.52 per-person, OR=1.22[1.18,1.27]) than the maintenance insomnia group.

**Conclusions:** Comparing to maintenance insomnia, those with onset insomnia have more abnormal neurodegenerative signs/symptoms. When evaluating neurodegenerative risk, differentiating the insomnia subtypes may help reliably discover prodromal neurodegenerative signs.

P 052

## Population exposure-response modeling of the effects of apomorphine sublingual film on QTc in patients with Parkinson's disease and "OFF" episodes

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**Objectives:** To characterize the relationship between plasma apomorphine concentrations and QTc (QT interval corrected for heart rate) in patients with Parkinson's disease (PD) and "OFF" episodes and predict changes in QTc from baseline at clinically relevant apomorphine concentrations.

**Methods:** Concentration-QTc models were developed from 447 time-matched apomorphine concentrations and electrocardiogram data from 39 patients with PD and "OFF" episodes who received placebo or apomorphine sublingual film (APL-130277; APL; 10-50 mg) in a thorough QT study using nonlinear mixed effects modeling methodology as implemented in NONMEM® software. QTc was assessed using Bazett's, Fridericia's (QTcF), and population (QTcP) correction methods. Various models were evaluated. The final model was used to predict changes in QTc from baseline at clinically relevant apomorphine concentrations.

**Results:** A final linear mixed effects model using QTcP with fixed effects for sex on baseline and random effects on intercept adequately described the relationship between apomorphine concentration and QTc interval. The slope of the QTcP-exposure relationship was minimal with a confidence interval (CI) that included zero (-0.0976 msec-mL/ng [95% CI: -0.8091, 0.6139]), indicating no strong correlation between QT prolongation and increasing apomorphine concentration. A sensitivity analysis with QTcF, which failed to adequately correct for heart rate, resulted in a slope estimate of the concentration-QTcF relationship of 0.274 msec-mL/ng (95% CI: -0.37, 0.92) and demonstrated a nonsignificant plasma concentration-QTc

relationship. At the highest proposed therapeutic dose of APL (35 mg), the estimate of the 95% CI upper bound for QTcP change from baseline was 4 msec at the maximum plasma concentration, which is below the regulatory threshold of 10 msec, indicating no clinically relevant effect of APL on QTc.

**Conclusions:** APL had no clinically relevant effect on QTc prolongation across the proposed therapeutic dose range of 10-35 mg.

## P 053

### Glucocerebrosidase mutations and phenoconversion of REM sleep behavior disorder to Parkinsonism and dementia

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**Objectives:** Mutations in the glucocerebrosidase (*GBA*) gene are strongly associated with REM sleep behavior disorder (RBD). It is unclear whether *GBA* mutations might affect clinical phenotype or rate of phenoconversion to parkinsonism or dementia. In this study, we investigated the role of *GBA* in determining clinical phenotype, phenoconversion of RBD to parkinsonism and dementia, and whether patients with *GBA* mutations are identifiable as an independent subtype of RBD.

**Methods:** We sequenced *GBA* in polysomnographic-proven idiopathic RBD (iRBD) patients. The effect of *GBA* mutations on clinical neurodegenerative markers and phenoconversion rate was assessed.

**Results:** Of 102 patients sequenced, 13 (13%) had *GBA* mutations and 89 did not. Aside from lower self-reported age of RBD onset in subjects with *GBA* mutations, no significant differences were observed in any clinical marker between patients with and without mutations. However, *GBA* mutations were associated with 3.3-fold higher phenoconversion rate from RBD to parkinsonism and/or dementia (95% CI=1.4-7.5,  $p=0.005$ ).

**Conclusions:** Although *GBA* mutations do not appear to affect clinical neurodegenerative markers (and thus are not differentiable as an independent subtype of iRBD), they nevertheless accelerate the conversion of RBD to defined neurodegenerative synucleinopathy.



P 054

## Gastric retention of the accordion pill™: Results from MRI studies with Parkinson's disease patients and healthy volunteers

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**Objectives:** To determine gastric retention (GR) of the Accordion Pill™ (AP) in patients with Parkinson's disease (PD) and healthy volunteers. While carbidopa/levodopa (CD/LD) is the gold standard treatment for PD, patients experience progressive motor fluctuations with ongoing treatment. Retaining LD in the stomach and gradually releasing it, may facilitate prolonged absorption, improving efficacy and safety while reducing daily dosing. AP-CD/LD is a novel drug delivery system based on GR of multilayer films containing immediate-release CD and both immediate- and controlled-release LD.

**Methods:** In an open label, randomized, 3-way crossover study (IN-08-004), patients with PD (18-75 y) received AP following their regular morning PD treatment. Three mechanically unique APs (weak, semi-weak, strong) were administered on test days with  $\geq 48$  h washout; meals were standardized. Magnetic resonance imaging (MRI) was conducted post-dose at 3, 5, 7, 9, 11, and 13 hours. In a second open label study, healthy volunteers received AP following overnight fasting; sequential MRIs were conducted every 1 h for 11 h, with breakfast and lunch standardized. Safety was assessed via adverse events (AEs).

**Results:** Of 18 patients enrolled, 83.3% were male and mean (SD) PD duration was 8.9 (4.6) y. Mean GR was 11.8 (7.3), 13.5 (5.8), and 13.9 (6.5) h for weak, semi-weak, and strong AP. In 11 healthy volunteers, the AP remained in the stomach for 8, 9, and 11 h in 100%, 91%, and 73% of participants. One serious AE (IN-08-004: general weakness/worsening of PD) was reported. Mild AEs of headache, nausea, and vomiting were reported in one participant and pain during MRI in another; all resolved.

**Conclusions:** AP GR was approximately 12 h in PD patients and 8 to 11 h in healthy volunteers. AP-CD/LD, currently in phase 3 development for PD, may improve efficacy and safety of LD treatment.

Funded by Intec Pharmaceuticals, LTD

P 055

## A pooled analysis for 8 randomized controlled trials of istradefylline, an adenosine A<sub>2A</sub> receptor antagonist: Efficacy as adjunct to levodopa in Parkinson's disease (PD)

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**Objectives:** Istradefylline, a well-tolerated selective adenosine A<sub>2A</sub> receptor antagonist, acts via the indirect basal ganglia outflow pathway. In 2013, 20 and 40mg/day doses were approved in Japan as adjunctive treatment to levodopa-containing products in PD patients experiencing wearing-off. Here we present a pooled efficacy analysis of 8 randomized, placebo-controlled studies of istradefylline combined with levodopa in PD patients experiencing motor fluctuations.

**Methods:** Istradefylline was evaluated in PD patients receiving levodopa with carbidopa or benserazide and experiencing motor fluctuations. Eight 12- or 16-week randomized, placebo-controlled, double-blind phase 2b/3 clinical studies were conducted globally (N=3245 subjects in total); change in OFF-time in daily, patient-completed 24-hour ON/OFF diaries provided the primary endpoint. All studies were designed to share a common methodology. Pooled analysis results from once-daily oral istradefylline (20 and 40mg/day) and placebo were evaluated using a mixed-model repeated-measures approach (including study as a factor).

**Results:** The pooled analysis included 2719 treated subjects (placebo, n=992; 20mg/day, n=848; 40mg/day, n=879). At week 12, OFF-hours/day with 20 and 40mg istradefylline were reduced (LS mean difference from placebo in reduction from baseline [95% CI], -0.38 [-0.61, -0.15] and -0.45 [-0.68, -0.22], respectively). ON-hours/day without troublesome dyskinesia increased from baseline with istradefylline compared with placebo (LS mean difference from placebo [95% CI], 20mg, 0.40 [0.15, 0.66]; 40mg, 0.33 [0.08, 0.59]). Five studies showed statistical improvement in OFF-time comparing istradefylline to placebo. Istradefylline was well-tolerated; average study completion rate was 89%. Dyskinesia was the most frequent adverse event (8% higher incidence with istradefylline than placebo). Additional secondary outcomes will be presented.

**Conclusions:** Istradefylline acts through an adenosine A<sub>2A</sub> receptor-mediated, non-dopaminergic mechanism for PD patients experiencing levodopa-mediated motor fluctuations. In the pooled analysis of 8 studies (and in 5 individual trials), istradefylline significantly improved OFF-time and ON-time without troublesome dyskinesia.

**Study supported by:** Kyowa Kirin Pharmaceutical Development, Inc.

P 057

## Is the personal Kinetigraph useful in the management of Parkinson's disease patients? A retrospective study from a tertiary movement disorder center

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**Objectives:** To assess the usefulness of the Personal KinetiGraph (PKG) in characterizing the intensity and timing of motor symptoms in Parkinson's Disease (PD) patients.

**Methods:** Retrospective study of all PD patients followed at a tertiary academic movement disorders center who were assessed by PKG between December 1, 2016 and October 30, 2018. The chart review recorded among other PKG indication and PKG impact on decision making. PKG indications included patient 1- was unable to give all characteristics of response to individual doses of medication, 2- did not feel any response to medication individual doses but overall felt better, 3- felt no response at all to medication, or 4- clinician wanted to verify the accuracy of patient's reported response to medications or 5- initiated treatment and wanted to objectively assess the response (ie no patient input at the time PKG was ordered).

**Results:** 170 total PKG sessions corresponding to 103 patients (61 males, average age 68.6) were examined. Average disease duration at PKG recording was 7 years. The indications for PKG sessions were as follows: 45 PKG for indication 1, 26 PKG for indication 2, 17 PKG for indication 3, 73 PKG for indication 4, and 9 PKG for indication 5. Of these indications, 67 PKG results allowed the physician to characterize response when patient was unable to give full answer. 65 PKG results allowed the physician to characterize motor symptoms differently than what the patient reported. 29 PKG results confirmed the patient's original report. 9 PKG results confirmed partial response to initial treatment requiring escalation in treatment.

**Conclusions:** In our series, PKG corrected or complemented patient input in 132 cases (77.6%) and confirmed it in 38 (22.4%), underlying the importance of characterizing and verifying patient's history via a wearable device such as PKG in order to optimize medical management.

P 058

## Long-term safety and effectiveness of istradefylline in patients with Parkinson's disease in a real-world setting: Results of a post-marketing surveillance study in Japan

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**Objectives:** Istradefylline is a first-in-class, non-dopaminergic, selective adenosine A<sub>2A</sub> receptor antagonist approved in Japan in 2013 as an adjunctive agent to levodopa (L-DOPA) in patients with Parkinson's Disease (PD) exhibiting the wearing-off phenomenon. We present results of a post-marketing surveillance (PMS) evaluating the long-term safety and effectiveness of istradefylline in patients with PD in a real-world setting.

**Methods:** We performed a PMS of patients who started treatment with istradefylline in Japan between May 30, 2013, and July 8, 2015, and the final data were registered on May 30, 2017. An electronic data capture system was used to record safety (adverse events and adverse drug reactions [ADRs]) and effectiveness (physician's assessment of off-time period, off-time symptoms and motor dysfunction, unified PD rating scale [UPDRS] Part III score, and physician's global assessment). We analyzed patients with follow-up data available up to 1 year after registration.

**Results:** Follow-up data were available for 476 patients (mean age 70.7 years; 45.8% male). The mean durations of PD symptoms and motor complications were 8.8 and 4.0 years, respectively, and 37.8% of patients presented with dyskinesia.

ADRs occurred in 20.8% of the enrolled patients. Among them, dyskinesia (5.0%), hallucination (3.4%), visual hallucination (1.3%) and somnolence (1.1%) were the most common, whereas other ADRs occurred in  $\leq 1\%$  of patients.

Over one-third of patients experienced a reduction in off-time (38.2%), and showed an improvement (or marked improvement) in off-time symptoms (44.7%) and in motor dysfunction (48.5%). The mean UPDRS Part III score decreased from 33.7 at baseline to 30.3 at the last available assessment. Istradefylline was rated as effective in 61.3% of patients according to the physician's global assessment.

**Conclusions:** This analysis of a PMS in Japan showed that istradefylline was well tolerated and effective in a real-world setting of PD patients exhibiting the wearing-off phenomenon with L-DOPA treatment.

## P 059

### Changes in optimal stimulation frequency with time for gait disturbances in patients with PD after STN DBS - a longitudinal study

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**Introduction:** Subthalamic nuclei deep brain stimulation (STN-DBS) improves many Parkinson's disease (PD) symptoms but gait disturbances can limit its usefulness. Stimulation frequency modification may help but its effectiveness over long term follow up is not clear.

**Aim:** To assess changes in frequency parameters of STN-DBS stimulation required to optimize gait in PD patients, over 6 months

**Methods:** 15 PD patients after STN-DBS with gait disorders were assessed during medication 'ON' state. Gait assessment using stand walk sit (SWS) test and freezing of gait (FOG) scores were done at baseline and after 6 months. Gait was assessed in five frequencies settings i.e., 60Hz, 90Hz, 130Hz, 180Hz and stimulation 'off'. Voltage was maintained. Completion time, number of steps, number of freezing episodes were analyzed in SWS. Wilcoxon signed rank test was used to analyze parameters.

**Results:** Mean age was  $58.47 \pm 11.35$  years, Mean duration of disease was  $11.00 \pm 4.18$  years. Mean duration after surgery was  $3.73 \pm 2.82$  years.

In SWS & FOG at base line, 5 patients had best response at 180Hz frequency, 5 at 130Hz, 1 at 90Hz, 2 at 60Hz, 1 both 60 and 90 Hz and 1 at both 90 and 180 HZ.

After 6 months, 2 patients became bedridden.

Among the remaining 13 patients, 4 patients had best response at 180 Hz frequency ,4 at 130 Hz ,2 at 90 Hz frequency, 1 each for 60 Hz frequency and battery off state ,1 for both 130Hz and 180 Hz.

Over 6 months, 4 patients had best response at the same frequency as base line, while 11 patients had change in frequency.

**Conclusions:** STN-DBS frequency for gait is not constant over time. This may be due to changes induced by the disease itself or plasticity induced by stimulation.

#### P 060

### Can we predict the functional impact of Parkinson's disease on daily activities measured by inertial sensors based on motor and non-motor symptoms?

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Parkinson's disease (PD) hinders the ability of a person to perform daily activities. However, the specific symptoms and interactions explaining the varying extent of the impact on a patient's motor repertoire is not understood.

**Objectives:** Investigate the possibility to predict global motor disabilities based on the symptomatology and medication. Specifically, we: (1) used clustering methods on performance metrics assessed for different motor tasks to reveal distinctive performance groups; and (2) developed and validated a multinomial regression model to predict the performance group membership based on the patient's condition.

**Methods:** 107 patients with PD equipped with a full-body inertial measurement system participated in this study. They accomplished different tasks such as eating soup, completing a timed up and go (TUG) test and performing the Purdue Pegboard test. K-means method was used for clustering the overall performance. Each participant also underwent a clinical evaluation of the symptoms, including bradykinesia, tremor, dyskinesia, rigidity, postural instability and cognitive deficit. A multinomial regression model was derived using 80% of the data, and validated with the remaining 20%.

**Results:** Clustering exposed four distinct performance groups: *normal* behaviour, slightly affected in fine motor tasks, affected only in TUG, and affected in all areas. The statistical model revealed that low-level dyskinesia increased the likelihood of being in the *normal* group. Increased postural instability increased the risk of being in the group affected in TUG only. Finally, LEDD did not help distinguishing between groups, but the presence of Amantadine as part of the medication regimen appears to decrease the likelihood of being part of the groups affected in TUG or fine motor task.

**Conclusions:** This approach is a step forward in the development of methods to predict the impact of the disease on a person's ability to perform daily activities based on clinical evaluation and medication regimen.

P 061

## Istradefylline, an adenosine A<sub>2A</sub> receptor antagonist, as adjunct to levodopa in Parkinson's disease: Safety analysis of 8 randomized controlled trials and 4 open-label long-term studies

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**Objectives:** Istradefylline, a selective adenosine A<sub>2A</sub> receptor antagonist, acts via the indirect basal ganglia outflow pathway. In 2013, doses of 20 and 40 mg/day were approved in Japan as adjunctive treatment to levodopa-containing products in adults with Parkinson's disease (PD) experiencing wearing-off phenomena. In placebo-controlled studies, istradefylline (20 and 40 mg/day) reduced OFF-time and increased ON-time without troublesome dyskinesia vs placebo. This report examines safety results from pooled analyses of placebo-controlled and open-label long-term studies of istradefylline plus levodopa in patients with PD experiencing motor fluctuations.

**Methods:** Safety was evaluated in 8 randomized, placebo-controlled double-blind 12- or 16-week phase 2b/3 studies and 4 open-label long-term studies. Patients with PD experiencing motor fluctuations during treatment with levodopa-containing products and possibly other standard anti-PD medications received adjunctive istradefylline or placebo. Assessments included treatment-emergent adverse events (TEAEs), physical (including neurologic) examinations, vital signs, weight, laboratory tests, and electrocardiograms.

**Results:** Placebo-controlled studies included patients receiving istradefylline (10-60 mg/day, fixed-dose, no titration; n=2073) or placebo (n=1010). TEAEs occurred in 72.4% of istradefylline-treated and 65.4% of placebo-treated patients. Dyskinesia was the most frequently reported TEAE (istradefylline 18%; placebo 10%). Other TEAEs occurring in >5% of istradefylline-treated patients included nausea, dizziness, and constipation. TEAEs led to similar treatment discontinuation rates between the istradefylline (6.5%) and placebo (5.2%) groups, with discontinuation rates due to dyskinesia of 1.3% and 0.7% (istradefylline and placebo, respectively). In long-term open-label studies (n=1893), patients received istradefylline for a median 53.3 weeks, with 62% treated ≥1 year. The pattern of TEAEs was similar between long-term and short-term treatment, with no additional adverse drug reactions identified.

**Conclusions:** Istradefylline offers an A<sub>2A</sub> receptor-mediated, nondopaminergic mechanism for patients with PD on levodopa and other conventional PD medications and was well-tolerated by patients with PD, with an acceptable safety profile.

**Study supported by:** Kyowa Kirin Pharmaceutical Development, Inc.

P 062

## **INFINITY directional leads: Initial “real world” experience in patients with movement disorders treated at the Cleveland Clinic, center for neurological restoration**

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**Background:** The introduction of directional Deep Brain Stimulation (DBS) leads offers potential for customized stimulation. However, reports of real world experience are not well described.

**Objectives:** To describe our initial programming experience with the St. Jude/ Abbott INFINITY Directional DBS Lead.

**Methods:** Consecutive patients at the Cleveland Clinic Movement Disorders program implanted with the INFINITY DBS Leads from April 2018 to December for Parkinson's Disease (PD) and Essential Tremor (ET) were analyzed. Initial and final programming settings were noted as well as lead orientation on post-operative x-rays.

**Results:** Twenty patients with PD (N=13) and ET (N=7) were included in this cohort, with a mean age of 68 (range: 53 to 78); 12 were men. Five unilateral and 15 bilateral leads were implanted for a total of 35 leads combining both STN (N=24) and VIM (N=11) targets. Post-operative imaging revealed 74% of the leads were rotated less than 90 degrees to the right. This information was critical to determining contact selection during the monopolar review. At final monopolar programming, the optimal setting, based on patient feedback and evaluation by an experienced programmer, required segmented contacts (i.e. directional stimulation pattern) in 80%, and non-directional (i.e. ring stimulation pattern) in 20% of the cases.

**Conclusions:** 1) The majority of the leads were rotated at the time of programming highlighting the importance of post-operative imaging. 2) Directional stimulation pattern was found to be optimal for most, but not all cases.

P 063

## **Safety and tolerability of opicapone in patients with parkinson's disease and motor fluctuations: Pooled analysis of two phase 3 studies**

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**Objectives:** To evaluate the adverse event profile of opicapone in adults with Parkinson's disease (PD). Catechol-O-methyltransferase (COMT) inhibitors were developed to prolong the clinical actions of levodopa in PD patients. Opicapone, a highly selective COMT inhibitor, is approved in Europe and under development in the U.S. as an adjunct to levodopa in adults with PD and motor fluctuations. In two international,

double-blind, placebo-controlled Phase 3 studies (BIPARK-1[NCT01568073], BIPARK-2[NCT01227655]), participants received once-daily opicapone (5mg [BIPARK-1 only], 25mg, 50mg), entacapone (BIPARK-1 only), or placebo for 14-15 weeks in addition to levodopa.

**Methods:** Preliminary analyses are presented using pooled data from BIPARK-1 and BIPARK-2. Participants who received entacapone or opicapone 5mg were not included in the pooled analysis. Assessments included treatment-emergent adverse events (TEAEs), TEAEs of special interest, laboratory, vital sign, and electrocardiogram (ECG) evaluations.

**Results:** The pooled analysis included 766 participants (placebo=257, 25mg=244, 50mg=265). Demographics and baseline characteristics were generally similar across treatment groups. No apparent dose-related effect was found for TEAE occurrence (placebo=57.2%, 25mg=62.3%, 50mg=64.2%), serious TEAEs (placebo=4.3%, 25mg=2.0%, 50mg=4.9%), or TEAEs leading to discontinuation (placebo=7.4%, 25mg=5.7%, 50mg=9.1%). Dyskinesia was the most common TEAE in all treatment groups (placebo=6.2%, 25mg=16.0%, 50mg=20.4%), but few participants had dyskinesia leading to discontinuation (placebo=0.4%, 25mg=0.8%, 50mg=3.0%) or serious dyskinesia (placebo=0%, 25mg=0.4%, 50mg=0.4%). None of the following were reported in opicapone-treated participants: serious/severe diarrhea, myocardial ischemia, or melanoma. No severe or serious hepatobiliary TEAEs were reported except for 1 case of acute cholecystitis (50mg); 2 subjects (25mg) reported urine discoloration. There were no clinically relevant differences between opicapone and placebo in laboratory parameters, vital signs, or ECGs.

**Conclusions:** Adding opicapone up to 50mg once daily to levodopa was generally well tolerated. TEAEs reported with other COMT inhibitors, such as hepatic injury and serious/severe diarrhea, were not observed. Final analyses will be presented at the meeting.

## P 064

### Pharmacokinetics of opicapone and effect on COMT and levodopa pharmacokinetics in patients with Parkinson's disease

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**Objectives:** To evaluate opicapone pharmacokinetics and pharmacodynamics in Parkinson's disease (PD). Opicapone, a highly selective COMT inhibitor, is approved in Europe and under development in the U.S. as an adjunct to levodopa in adults with PD and motor fluctuations.

**Methods:** Patients with stable PD received once-daily opicapone (50mg) in the evening on Days 1-14. Serial blood samples for determining plasma opicapone concentrations and erythrocyte soluble COMT (S-COMT) activity were collected after the first and last opicapone dose. Participants were randomized to receive carbidopa/levodopa (25/100mg) every 3 or 4 hours (Q3H or Q4H) on pharmacokinetic sampling days, and their usual carbidopa/levodopa regimen on other days. Serial plasma samples for determination of levodopa and 3-O-methyldopa concentrations were collected after the first three levodopa doses on Day1 (prior to opicapone dosing), Day2 and Day15. The effect of opicapone on levodopa pharmacokinetics and S-COMT activity was assessed. Mean values ( $\pm$ standard errors) are presented.



**Results:** The study enrolled 16 participants (men=10, women=6). Day 14 opicapone  $C_{max}$  and  $AUC_{0-last}$  were  $459 \pm 63$  ng/mL and  $2022 \pm 196$  ng\*hr/mL, respectively. At steady-state (Day14), COMT activity was inhibited on average by  $76.3 \pm 1.4\%$ , compared to baseline. After opicapone administration, total levodopa AUC (ng\*hr/mL) increased from Day1 (Q3H,  $7339 \pm 949$ ; Q4H,  $7570 \pm 946$ ) to Day15 (Q3H,  $11714 \pm 1674$ ; Q4H,  $13159 \pm 1509$ ). Peak-to-trough fluctuation in levodopa concentrations for the third daily levodopa dose were reduced from  $88.3 \pm 15.2\%$  and  $173 \pm 18.3\%$  for the Q3H and Q4H regimens on Day1 to  $58.1 \pm 8.7\%$  and  $94.3 \pm 9.2\%$ , respectively, on Day15. Trough levodopa concentrations for the third daily levodopa dose increased from  $547 \pm 51$  and  $227 \pm 28$  ng/mL for the Q3H and Q4H regimens on Day1 to  $1142 \pm 201$  and  $749 \pm 125$  ng/mL, respectively, on Day15.

**Conclusions:** Once-daily opicapone 50mg resulted in substantial and prolonged COMT inhibition, which increased systemic exposure to levodopa and led to decreased peak-to-trough fluctuations in levodopa concentrations and to higher trough levodopa concentrations.

## P 065

### Effect of age on efficacy and safety of levodopa-carbidopa intestinal gel for advanced Parkinson's disease: Interim analysis of the DUOGLOBE Study

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**Objectives:** Assess effect of age on efficacy/safety of levodopa-carbidopa intestinal gel (LCIG) in patients with advanced Parkinson's Disease (APD). Data on routine clinical use of LCIG in APD patients with different ages are limited.

**Methods:** In this interim analysis of the post-marketing observational study, DUOGLOBE, outcomes are assessed within age groups: < 65 years, 65-75 years, and >75 years. Outcomes include mean change from baseline in OFF time, dyskinesia (UDysRS), activities of daily living (UPDRS II), quality of life (PDQ-8), non-motor symptoms (NMSS), sleep (PDSS-2), and caregiver burden (MCSI). Serious Adverse Events (SAEs) are monitored.

**Results:** The current sample included 30/64/45 patients at baseline for the subgroups < 65 years, 65-75 years, and >75 years; N=15-24/33-49/22-27 for month 6 depending on outcome. At 6 months, OFF time was significantly reduced by 3.5, 3.1, and 4.2 hours in patients aged < 65 years, 65-75 years, and >75 years, respectively. UDysRS showed significant improvement at month 6 by 18.3, 10.8 and 17.7 points in the three age subgroups. NMSS improved significantly by 49.8, 17.6, and 41.5 points at month 6 across these subgroups. PDSS-2 scores at month 6 improved by 8.4, 1.7 and 6.8 points for patients < 65 years, 65-75 years, and >75 years. Similar improvements were observed for PDQ-8. Variable results were observed for UPDRS II and MCSI scores. SAEs occurred more frequently in patients with higher age (< 65: 16.7%; 65-75: 29.7%; >75: 33.3% of patients) with similar rates of AEs leading to withdrawal of drug in all subgroups (10%; 9%; 13%).

**Conclusions:** In this interim analysis of a multinational observational study, LCIG treatment led to improvement in motor and non-motor symptoms in patients of different ages. SAE rates were higher in patients >75 years. These data are limited by small sample sizes, and further analysis is warranted.

P 066

## Symptom improvements with once-daily opicapone in patients with Parkinson's disease and motor fluctuations: Pooled subgroup analysis of two phase 3 studies

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**Objectives:** Opicapone, a highly selective catechol-O-methyltransferase (COMT) inhibitor, is approved in Europe and under development in the U.S. as an adjunct to levodopa in adults with PD and motor fluctuations. Data from two phase 3 studies (BIPARK-1[NCT01568073], BIPARK-2[NCT01227655]) were pooled to evaluate the effects of once-daily opicapone on OFF-time in the overall population and within patient subgroups.

**Methods:** BIPARK-1 and BIPARK-2 participants were randomized to 14-15 weeks of double-blind placebo-controlled treatment with opicapone or placebo added to their levodopa regimen. Based on the primary endpoint in both studies, least squares (LS) mean changes from baseline to Week 14/15 in daily absolute OFF-time were analyzed in the pooled population and in subgroups defined by the following baseline factors: age, gender, race, modified Hoehn and Yahr (H&Y) stage during ON, and concurrent PD medication use (dopamine agonists [DA] or monoamine oxidase-B inhibitors [MAOBI]). Analyses were conducted using a mixed-model for repeated measures. Results for the targeted opicapone clinical dose (50mg) are presented.

**Results:** In the overall pooled population (placebo=255, 50mg=262), LS mean changes ( $\pm$ standard error [SE], hours) in OFF-time were as follows: placebo,  $-1.28 \pm 0.17$ ; 50mg,  $-2.22 \pm 0.17$  ( $P < 0.001$ ). A statistically significant decrease (improvement) in absolute OFF-time from baseline to Week 14/15 was observed with opicapone 50mg in all of the following subgroups: placebo-corrected LS mean changes ( $\pm$ SE): age ( $< 65$  years,  $-0.71 \pm 0.31$ ;  $\geq 65$  years,  $-1.16 \pm 0.33$ ), gender (men,  $-0.94 \pm 0.29$ ; women,  $-0.97 \pm 0.35$ ), race (white,  $-0.87 \pm 0.25$ ; Asian,  $-1.15 \pm 0.55$ ), H&Y (score  $< 2.5$ ,  $-1.00 \pm 0.40$ ; score  $\geq 2.5$ ,  $-0.89 \pm 0.27$ ), DA use (yes,  $-0.93 \pm 0.26$ ; no,  $-1.01 \pm 0.44$ ), MAOBI use (yes,  $-1.14 \pm 0.50$ ; no,  $-0.90 \pm 0.25$ ); all  $P < 0.05$  versus placebo.

**Conclusions:** Once-daily opicapone 50mg significantly reduced daily OFF-time compared to placebo in patients with PD and motor fluctuations. The improvement was observed consistently across patient subgroups regardless of age, gender, race, H&Y stage, and concurrent DA or MAOBI use.

P 067

## Pharmacokinetics of multiple doses of Accordion Pill™ carbidopa/levodopa in patients with Parkinson's disease

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**Objectives:** To perform a pharmacokinetic (PK) assessment of a novel carbidopa/levodopa (CD/LD) drug delivery system (Accordion Pill™; AP-CD/LD) and to determine if AP-CD/LD can provide relatively continuous delivery of LD compared with immediate-release (IR)-CD/LD in patients with Parkinson's disease (PD).

**Methods:** This open-label crossover study compared the PK of AP-CD/LD 50mg/500mg dosed three times daily (TID) with 1.5 tablets of standard IR-CD/LD 25mg/100mg dosed 5x daily. Eligible participants presented to the clinic on day 1 in the practically-defined OFF state and were treated with standard IR levodopa at 3-hour intervals. PK assessments were performed every 30 minutes for 16 hours and again at 24 hours. Participants were discharged and instructed to take AP-CD/LD 50mg/500mg TID at 5-hour intervals for the next 7 days. Participants returned to the clinic on day 8 and received AP-CD/LD at 0, 5, and 10 hours. PK assessments were performed as described for day 1. The primary endpoint was LD fluctuation index ( $[C_{\max} - C_{\min}] / C_{\text{average}}$ ) at steady state (4-16 hours). A key secondary endpoint was LD coefficient of variation at steady state. Day 8 and day 1 results were compared (paired t-test). Adverse events were recorded.

**Results:** Twelve PD patients participated in the study. Treatment with AP-CD/LD TID resulted in significantly less variability in LD plasma concentration versus standard IR-CD/LD therapy, with a mean difference in fluctuation index (95% confidence interval) of 0.63 (0.24-1.03;  $P=0.005$ ). Similar results were observed for all sensitivity analyses and for the key secondary endpoint of the LD coefficient of variation ( $P=0.047$ ). No adverse events were reported with AP treatment.

**Conclusions:** As reduced variability in plasma LD concentration has been associated with reduced motor complications, these preliminary results suggest that treatment with AP-CD/LD may reduce motor complications compared with standard IR-CD/LD treatment in advanced PD patients.

Funded by Intec Pharma, LTD

P 068

## Patient-centered outcomes of deep brain stimulation in parkinson's disease

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**Objectives:** DBS long-term outcomes have demonstrated sustained improvement in motor symptoms of Parkinson's disease. Few studies have evaluated patient-centered outcomes (PCO). We aimed to evaluate PCO after DBS in PD patients.

**Methods:** A PCO questionnaire was administered to PD patients post-DBS. The questionnaire measured outcomes on mobility, gait, postural instability, cognitive, speaking, psychiatric symptoms, sexual functions, pain, social life, and issues related to the DBS device. All questions were scored on a five-point Likert scale. Demographic and clinical data before surgery was collected.

**Results:** Forty-seven patients answered the questionnaire (55.3% males). Mean age was 58.3y (SD 8.7). Mean H&Y stage was 3.3 (SD 0.6), and mean DBS therapy duration was 25.5 months. Subthalamic nucleus (STN) was the target in 38 (80.8%), and Forel's field in 9 patients. *Mobility:* 89.4% of patients agreed that DBS improved walk velocity in small distances (100 m), and 80.9% agreed that DBS facilitated walk (1 km). *Postural instability:* 85.1% of patients agreed they have better balance and 76.6% agreed they have less falls. *Pain* was reduced in 68.1% of patients, and *sexual performance* was better for 42.6%. *Anxiety* was reduced for 72.3% of patients, whereas *depression* was reduced for 80.8%. Most patients (80.6%) agreed they feel better during *social activities*. On the other hand, 42.6% experienced worsening of *speaking*. DBS device was not a problem for 85.1%. A multivariable regression analysis showed younger age as a predictive factor for good outcomes after DBS surgery. Overall mean grade (0 to 10) for patient satisfaction with DBS therapy was 8.9, and 96.7% would undergo the surgical treatment again.

**Conclusions:** After an average of two years post-DBS surgery, the majority of patients were satisfied, felt they had made the correct decision to undergo DBS, and would choose to have DBS again. Younger age predicted high level satisfaction.

## P 069

### Population exposure-response models of apomorphine sublingual film in healthy subjects and patients with Parkinson's disease and "OFF" episodes

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**Objectives:** Exposure-response models were developed to characterize the relationship between apomorphine exposure and (1) efficacy using Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III score in patients with Parkinson's disease (PD) and "OFF" episodes, (2) systolic/diastolic blood pressure (sBP/dBP) in healthy subjects/patients, and (3) nausea/oral adverse events (AEs) in patients following apomorphine sublingual film (APL-130277; APL) administration.

**Methods:** Data were analyzed using nonlinear mixed effects modeling methodology as implemented in NONMEM<sup>®</sup> software. Final model simulations estimated apomorphine concentration and its association with MDS-UPDRS Part III score. For BP, nominal time-matched data were evaluated by linear and maximum effect models. Time-to-event and extended Cox proportional hazard models described nausea/oral AEs.

**Results:** For efficacy, a 23-point decrease from baseline in MDS-UPDRS score was estimated as the inhibitory maximum effect; a cutoff of  $\leq -12.5$  points was associated with a FULL "ON" response; response duration increased from 1.6-3.1 hours for a 10-mg and 35-mg dose of APL, respectively; and average apomorphine concentrations of 2.66-2.94 ng/mL correspond with these outcomes. For BP, single doses of 10

and 35 mg APL were predicted to decrease sBP by 3 and 7 mmHg, respectively, and dBP by 1 and 3 mmHg, respectively; decreases were more prevalent in patients than in healthy subjects. For AEs, predicted risk of nausea (hazard ratio, 2.01) and oral events (hazard ratio, 1.34) were higher for single doses of APL 35 vs 10 mg, respectively.

**Conclusions:** Longitudinal and time-to-event exposure-response models demonstrated a correlation between apomorphine exposure and efficacy using MDS-UPDRS Part III score. Increases in apomorphine plasma concentration were associated with a modest decrease in sBP/dBP, and an increase in risk for nausea and less so for oral AEs following administration of sublingual apomorphine in patients with PD and “OFF” episodes.

P 070

### **Levodopa-carbidopa intestinal gel treatment of motor fluctuations and dyskinesia in advanced parkinson's disease patients in a 'real world' setting: Interim results from the DUOGLOBE Study**

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**Objectives:** Assess the long-term effectiveness of levodopa-carbidopa intestinal gel (LCIG) on motor fluctuations and dyskinesias in advanced Parkinson's disease (PD) patients treated in routine clinical practice.

**Methods:** DUOGLOBE is the first multinational observational routine care study of LCIG with 3-years follow-up. Primary outcome is mean change in patient-reported “Off” time; secondary outcomes include motor complications (dyskinesia duration and severity), as measured by the recently developed Unified Dyskinesia Rating Scale (UDysRS). Outcomes were collected at baseline, day (D) 1 and scheduled visits closest to months (M) 3, 6, and 12 (±14 days) in this interim analysis.

**Results:** 139 patients were included in the analysis (78% ≥65 years old; 51% ≥10 years' disease duration and sample sizes became limited over time. LCIG treatment significantly reduced patient-reported “Off” time (mean decrease from baseline to M12: -4.1 hours) irrespective of sex, age, and disease duration. Dyskinesia assessed by UDysRS significantly improved at D1 and was maintained through M12 (mean decrease from baseline: -12.7). Improvements according to UPDRS part IV scores for duration of “Off” time (through M12), dyskinesia duration (through M6), dyskinesia-related disability (through M12), and dyskinesia-related pain (through M12) were also observed. Safety was consistent with LCIG's known profile.

**Conclusions:** This interim analysis confirms the marked improvement in "Off" time with LCIG in routine clinical practice. This first analysis using UDysRS, and supporting data from UPDRS part IV, showed that LCIG treatment was also associated with a marked reduction in dyskinesia duration and severity. These findings provide further evidence for the real-world effectiveness of LCIG on motor fluctuations and duration and severity of dyskinesia.

#### P 071

### Real world clinical outcomes using a novel directional lead from a multicenter registry of deep brain stimulation for Parkinson's disease

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**Objectives:** Deep Brain Stimulation (DBS) systems have historically used ring-shaped electrodes that produce stimulation fields with limited control over field shape and volume of tissue activated. Directional current steering may permit a more personalized DBS approach with respect to individualized shape and pattern of electrical field and corresponding volume of tissue activated.

**Methods:** The Vercise DBS Registry (ClinicalTrials.gov Identifier: NCT02071134) is a prospective, on-label, multi-center, international registry sponsored by Boston Scientific. Subjects in this cohort were implanted with a directional lead included as part of a multiple-source, constant-current directional DBS system (Vercise Cartesia, Boston

Scientific). Subjects were followed up to 3-years where their overall improvement in quality of life and PD motor symptoms was evaluated. Adverse events were collected.

**Results:** To date, 200 enrolled patients have been implanted with the directional lead. Improvement in Quality of Life following DBS implant with the directional lead was demonstrated at 6 months and 1-year post implant. Improvements in motor function (change in MDS-UPDRS III scores - meds off condition) was also noted. Additional data is to be presented.

**Conclusions:** Enabling fractionalization of current using MICC can permit application of a well-defined, shaped, electrical field. This on-going registry represents the first comprehensive, large scale collection of real-world outcomes using a directional lead and an MICC-based DBS system.

P 072

## **Dyskinesia and OFF prevalence: Population profile throughout the day and effect of Gocovri on frequency and duration of episodes relative to placebo**

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**Objectives:** Use PD patient diary data from phase 3 trials to assess the pattern of dyskinesia and OFF prevalence throughout the day, and to measure the effect of Gocovri™ (amantadine) extended release capsules in reducing daily OFF and dyskinesia episodes relative to placebo.

**Backgrounds:** PD patients develop episodes of OFF and troublesome dyskinesia throughout the day, affecting quality of life and social participation. Gocovri is the only FDA-approved pharmacological agent demonstrated to reduce both dyskinesia and OFF in PD patients. To our knowledge, no studies have mapped the prevalence of these states throughout the day or the effect of adjunctive therapy on daily episodes.

**Methods:** Novel analysis of pooled data from EASE LID and EASE LID 3, reported as time spent in each diary state (in 30-minute intervals) over 24 hours, provided time profiles synchronized to participants' wakeup time, at baseline and Week 12. Prevalence of patients in each diary state per interval, and changes in OFF and troublesome dyskinesia episode frequency and duration were measured. Safety data were also summarized.

**Results:** Of 196 patients enrolled, 162 (82.7%) provided evaluable diaries at baseline and week 12. At baseline, 67% of patient woke up in the OFF state, and approximately 15% of patients experienced OFF during each 30-minute interval thereafter. From 2-15 hours following wake-up, 24% to 44% of patients reported troublesome dyskinesia during each 30-minute interval. Mean number/duration (hours) of troublesome dyskinesia and OFF episodes at baseline were 3.0/2.0 and 2.2/1.0, respectively, and were reduced by Gocovri relative to placebo, with treatment differences of -1.0/-0.6 and -0.4/-0.3 at week 12.

**Conclusions:** Troublesome dyskinesia and OFF were prevalent in the morning and throughout the waking day. Gocovri-treated patients experienced fewer, shorter episodes of both states relative to placebo, with longer episodes of Good ON time and fewer transitions between motor states.

P 073

## Patient-reported “good” days during a prospective study of the treatment of neurogenic orthostatic hypotension with droxidopa

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**Objectives:** To evaluate the effect of droxidopa treatment on patient-reported assessments of a “good” or “bad” day in patients with neurogenic orthostatic hypotension (nOH)

**Backgrounds:** Droxidopa is approved in the United States to treat symptomatic nOH in adults. Common symptoms of nOH include lightheadedness and dizziness, which can lead to an increased likelihood of falls. Patients with nOH may experience decreased functional ability and an increased fear of falling, which can cause feelings of depression and anxiety, leading to social isolation.

**Methods:** In a 6-month prospective cohort study of patients with nOH newly initiating droxidopa treatment, participants were asked to quantify the number of good and bad days in the past week. Participants also reported outcomes using other validated instruments that measure nOH symptoms (Orthostatic Hypotension Symptom Assessment Item 1), functional impairment (Sheehan Disability Scale), depressive symptoms (Patient Health Questionnaire-9), fear of falling (Falls Efficacy Scale-International), and health-related quality of life (HRQoL; Short Form-8). Scores after 1 and 6 months of treatment were compared with baseline.

**Results:** After 1 month of droxidopa treatment, patients reported a significant increase in good days from baseline (mean, 4.2 vs 3.3 days/week; difference, 0.9 days/week;  $P < 0.0001$ ). Similarly, a significant increase in reported good days was observed at 6 months vs baseline (mean, 4.5 vs 3.4 days/week; difference, 1.1 days/week;  $P < 0.0001$ ). The significant increase in good days at 1 and 6 months correlated with improvements in other patient-reported outcomes of nOH symptoms, fear of falling, functional impairment, depressive symptoms, and HRQoL (all  $P < 0.0001$ ).

**Conclusions:** Patients treated with droxidopa reported significantly more good days per week compared with before treatment initiation. The increased number of good days tracked with improvements in other patient-reported indicators of mental wellbeing. Improved patient perception of psychological status may represent an important downstream holistic benefit of nOH treatment.



P 074

## Development of a minimum neuropsychological and non-motor assessment battery for PD patients undergoing DBS

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**Objectives:** To describe the development of a neuropsychological and non-motor symptom assessment battery for Parkinson's disease (PD) patients undergoing deep brain stimulation (DBS) surgery.

**Methods:** The Registry for Advancement of Deep Brain Stimulation in PD (RAD-PD) is a multi-center quality improvement (QI) patient registry designed to investigate the best practices, adverse effects, health economics and outcomes disparities relating to DBS in PD, with the ultimate goal of improving patient outcomes. A multi-disciplinary planning committee consisting of movement disorders neurologists, neurosurgeons, neuropsychologists, and patient advocates identified clinician-measured and patient-reported outcomes (PROs) that will facilitate registry goals. The committee reviewed existing literature, the NIH Common Data Elements, HealthMeasures, International Consortium for Health Outcomes Measurement, MDS Task Force reports, and existing DBS, PD and surgical registries to identify a minimum dataset that would assess the most relevant neuropsychological and non-motor symptoms while minimizing site burden and maximizing use of PROs.

**Results:** The RAD-PD dataset will include assessment of cognition, quality of life, activities of daily living, mood, sleep, hallucinations, and autonomic issues, amongst others, employing standard and non-routine scales. At baseline, neuropsychological screening measures and PROs that may aid in determining patient selection for DBS will be captured. QI efforts will benchmark which pre-operative measures correlate best with patient outcomes. At follow-up visits (6mos and annually to 5 years), additional measures will help identify outcomes disparities for which etiologies or predictors can then be investigated. RAD-PD also recommends a battery of optional neuropsychological measures to collect standardized comprehensive cognitive data longitudinally in a large well- characterized multi-center cohort.

**Conclusions:** A minimum data set and QI efforts in RAD-PD have the potential to yield practice recommendations for which there is currently an insufficient evidence base, including identification of best practices for patient selection based on motor and non-motor symptoms and for post-operative management.

P 075

## What impacts the caregiver burden in Parkinson's disease?

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**Background:** The caregivers of Parkinson's disease (PD) patients have a highly demanding responsibility. Our study aims to investigate the impact of motor and non-motor symptoms on caregiver burden among PD patients.

**Methods:** PD patient-caregiver pairs were recruited. Patients were evaluated on motor, non-motor symptoms and quality of life (QoL). Caregivers' burden was stratified into 3 subgroups. Statistical analysis was performed to identify differences in the no-or little, mild-moderate and high caregiver burden subgroups.

**Results:** Compared to mild-moderate, the high caregiver burden subgroup consisted of patients with more progressive disease (mean duration 9.63 versus 6.12 years;  $p=0.004$ ), 56.3% were Hoehn & Yahr Stage  $\geq 3$ , with mean LEDD of 556mg and more frequent and severe mood symptoms (NMSS-Mood Domain median score 8.0 versus 1.0;  $p=0.009$  and PDQ39-Emotional Wellbeing Domain 35.4 versus 16.7;  $p=0.014$ ). The mild-moderate versus no-or little subgroups showed a marked increase in PDQ39 self-reported mobility issues (40.0 versus 22.5;  $p=0.015$ ), ADL dependency (25.0 versus 8.3;  $p=0.005$ ) and higher NMSS Sleep/fatigue scores (8.0 versus 5.0;  $p=0.044$ ).

**Conclusion:** Greater caregiver burden was more likely in patients with more progressed disease, poorer therapeutic control of motor symptoms, and more frequent and severe mood symptoms.

P 076

## Combined mGlu<sub>2</sub> positive allosteric modulation and mGluR<sub>2</sub> orthosteric stimulation attenuates dyskinesia and psychosis in the Parkinsonian marmoset

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**Objectives:** To investigate the effect of combined metabotropic glutamate 2 (mGlu<sub>2</sub>) receptor positive allosteric modulation and orthosteric stimulation on L-3,4-dihydroxyphenylalanine (L-DOPA)-induced psychosis-like behaviours (PLBs) and dyskinesia in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned marmoset model of Parkinson's disease (PD).

**Methods:** Six common marmosets were rendered parkinsonian by MPTP injection. PLBs and dyskinesia were induced following repeated administration of L-DOPA/benserazide (L-DOPA). Then, they were administered acute challenges of LY-487,379 (1 mg/kg), LY-354,740 (1 mg/kg), LY-487,379/LY-354,740 (each 1 mg/kg) or vehicle, in combinaison with L-DOPA, after which the severity of PLBs, dyskinesia and parkinsonian disability were determined.

**Results:** LY-487,379, LY-354,740 and LY-487,379/LY-354,740 each significantly reduced the severity of the global dyskinesia score, by  $\approx 42\%$ ,  $55\%$  and  $64\%$  (each  $P < 0.001$ ), when compared to L-DOPA/vehicle. The combination LY-487,379/LY-354,740 was significantly more effective than either treatment alone (both  $P < 0.05$ ). The severity of the global PLB score was also significantly reduced by each of LY-487,379, LY-354,740 and LY-487,379/LY-354,740, by  $\approx 51\%$ ,  $44\%$  and  $56\%$  (each  $P < 0.001$ ), when compared to L-DOPA/vehicle. The combination LY-487,379/LY-354,740 was significantly more effective than LY-487,379 ( $P < 0.01$ ), but not LY-354,740 ( $P > 0.05$ ). The benefits on dyskinesia and PLBs were achieved without compromising the therapeutic effect of L-DOPA on parkinsonism.

**Conclusions:** Our results confirm mGlu<sub>2</sub> activation, via both positive allosteric modulation and orthosteric stimulation, is a promising strategy to effectively reduce dyskinesia and psychosis in PD without impairing the therapeutic efficacy of L-DOPA. Moreover, they suggest that the combination of a positive allosteric modulator and an orthosteric agonist may lead to a synergistic effect, thereby providing greater anti-dyskinetic and anti-psychotic effects.

## P 077

### Effects of sugar control on motor manifestations in Parkinson's disease with diabetes mellitus

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**Background and Purpose:** Converging evidences indicated close relationships between Parkinson's disease (PD) and diabetes mellitus (DM). The prevalence of PD is relatively high in patients with DM, and PD patients have higher risk of altered glucose metabolism or increased insulin resistance. The present study investigated the effects of sugar control in motor manifestations of de novo PD patients.

**Methods:** Consecutively recruited 57 de novo PD patients who were also diagnosed with DM were classified into either group of well-controlled ( $n = 24$ ) or poorly controlled DM ( $n = 33$ ) by cut-off value of 7.0 of HbA1c. Age and Unified Parkinson's Disease Rating Scale (UPDRS) III scores were matched between two groups, and alterations of UPDRS III scores were compared over 1 year of follow up.

**Results:** The well-controlled DM group showed significantly better improvement of UPDRS III scores (baseline to 1 year after,  $37.4 \pm 9.2$  to  $24.3 \pm 6.5$ ) compared to poorly controlled group ( $37.8 \pm 10.6$  to  $30.2 \pm 7.2$ ) over 1 year of follow up (gap of UPDRS III score,  $-13.2 \pm 9.2$  vs  $-7.2 \pm 6.9$ ;  $p, 0.013$ ). Higher HbA1c were highly associated with lesser improvement of UPDRS III scores ( $r, -0.563$ ; 95 % CI,  $0.216 - 0.784$ ;  $p, 0.003$ ).

**Conclusions:** Our data demonstrated that poorly controlled DM might have detrimental effect on motor improvements in patients with PD. Strict sugar control could be a promising strategy to improve motor manifestation in PD.

P 078

## Impact of residual drug in the pharynx for the cause of delayed-on phenomenon in Parkinson's disease patients

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**Background:** Delayed-on phenomenon (DOP) related to levodopa treatment frequently occurred and disturbed quality of life in the advanced stage of Parkinson's disease (PD).

**Objectives:** The aim of this study was to explore the impact of swallowing dysfunction for the development of DOP.

**Methods:** We investigate swallowing function by using endoscopic evaluation in ten PD patients with the DOP and seven PD patients without the DOP. We evaluate structural abnormality in the hypopharynx, pooling of saliva, delayed swallowing reflex as well as awareness of dysphagia and penetration aspiration scale. We also observe residual drug in the pharynx after taking tablet, capsule and powder type of drug.

**Results:** The frequency of residual drug in the pharynx was seen in five cases (29.4%). Residual drug was more frequent in cases with the DOP group than without the DOP ( $p=0.02$ ). Other factors related in swallowing function were not related to the presence of DOP. The odds ratio of the DOP in patients with residual drug was 46.20 (95% CI: 1.87-1141.25).

**Conclusions:** The results of this study suggest that swallowing dysfunction leading to residual anti-parkinsonian drug in the pharynx has great impact for DOP in PD patients.

P 079

## Intrajejunal levodopa infusion for Parkinson's disease: A Canadian experience

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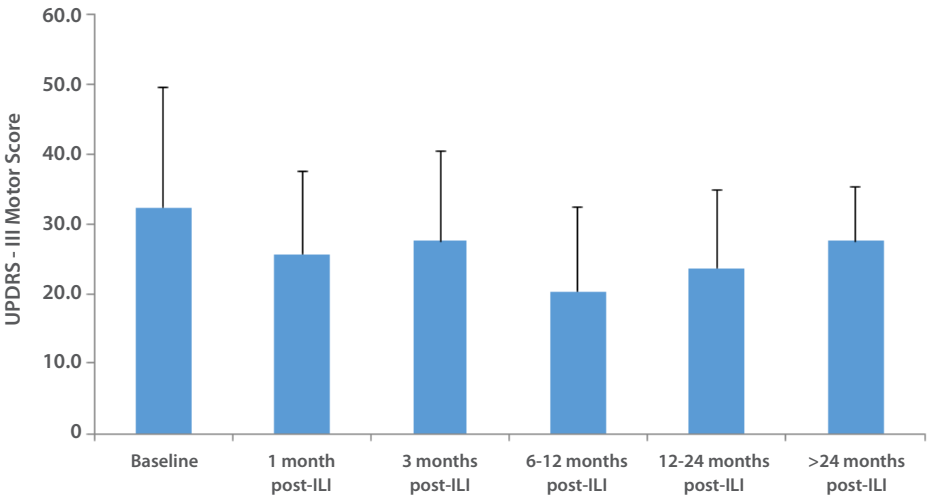
**Background:** Intrajejunal levodopa infusion (ILI) therapy is a safe and effective drug delivery method for patients with advanced Parkinson's disease (PD) delivered through percutaneous endoscopic gastrostomy with jejunal extension (PEG-J). Since it was introduced in Canada in 2011, little is known about the long-term benefits and complication rates.

**Methods:** Retrospective chart review was done of patients who underwent ILI in the Movement Disorders program at the University of Alberta over the last 8 years. Data collected included dosing, UPDRS-III motor scores, OFF times, hours with dyskinesias per day, MoCA scores, complications, medication side effects, and nursing time requirements.

**Results:** Twenty-six patients underwent PEG-J insertion for ILI over the last 8 years. Following ILI initiation, at 24 months ( $n = 10$ ), reductions were seen in UPDRS-III motor subscore by 24%, OFF times by 38%, and dyskinesias by 70% from baseline. Benefit was maintained for up to 4 years. Complications included stoma

discharge (7 patients), infection (5 patients), duodenal pressure ulceration (1 patients), and peripheral neuropathy (2 patients). On average, 1 PEG-J dislodgement per patient per year requiring replacement was seen, with one patient having 9 dislodgements over 3 years. Since 2011, discontinuations occurred due to: inadequate effect (4), death (2), development of severe dementia (2), or transition to deep brain stimulation (2). Nursing time averaged at 22 hours per patient per year.

**Conclusions:** Most patients on ILI had improved motor scores with reduced OFF-times and dyskinesias with prolonged follow-up. ILI treatment should be performed by an inter-disciplinary team of experienced healthcare professionals who can anticipate and promptly address complications that arise in this setting.



*[UPDRS Scores pre- and post-initiation of ILI therapy]*

P 080

## A thorough QT study of apomorphine sublingual film in patients with Parkinson's disease complicated by "OFF" episodes

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**Objectives:** To assess the effect of apomorphine sublingual film (APL130277; APL) on the QT interval in patients with Parkinson's disease (PD) and "OFF" episodes participating in a Phase 2, randomized, double-blind, placebo-controlled study.

**Methods:** Adult patients with PD and "OFF" episodes, no cardiac abnormalities, and no antiemetic use on stable PD medications were eligible. Forty patients were randomized to a single dose of APL (dose determined during titration), matching placebo, and moxifloxacin (positive control; 400 mg) in a 3-way crossover design. Time-matched changes from baseline in the placebo-adjusted QT interval corrected using Fridericia's formula ( $\Delta\Delta QTcF$ ), were calculated from electrocardiograms taken at 0.25, 0.5, 0.75, 1, 2, 3, and 4 hours postdose. Baseline was defined as the mean of 9 predose measurements.

**Results:** The lower limit of the Bonferroni-corrected 90% confidence intervals for the moxifloxacin-placebo comparison was above the 5 ms threshold at 3 of the 4 prespecified timepoints, demonstrating adequate sensitivity to assess QT interval corrected for heart rate prolongation.

**Conclusions:** This is the first study to evaluate apomorphine delivered as a sublingual film on QT interval and other parameters of cardiac conduction in patients with PD and "OFF" episodes. The results from these analyses will be subsequently presented.

P 081

## Assessing tele-health outcomes in multiyear extensions of Parkinson's disease trials (AT-HOME PD): Initiation of a long-term observational study

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**Objectives:** To develop, implement, and evaluate a model for the remote, long-term observation of Parkinson's disease (PD) clinical research cohorts. Mobile and remote technologies will potentially improve clinical trial efficiency through frequent, long-term data collection, objective assessment in a realistic set-

ting, and the possible development of digital biomarkers. We will 1) implement the infrastructure for a new research model, 2) compare patient- and clinician-reported outcomes, and 3) develop novel biomarkers of PD disability and progression.

**Methods:** AT-HOME PD aims to enroll an estimated 420 participants from two NINDS-funded phase 3 interventional studies of potential disease-modifying therapeutics for PD (STEADY-PDIII and SURE-PD3). This 24-month observational study will remotely characterize long-term clinical outcomes using three platforms: virtual research visits conducted annually by centralized movement disorder specialists, smartphone-based motor tasks performed quarterly in two-week sessions by participants using mPower, and web-based surveys completed quarterly in an online companion study (Fox Insight). For consented participants, mPower passively collects GPS- and accelerometer-based movement and activity data. Data from the three platforms and the parent studies will be integrated and transferred to the Parkinson's Disease Biomarkers Program's Data Management Resource for use by the broader research community.

**Results:** From the parent studies, 266 STEADY-PDIII and 201 SURE-PD3 participants have thus far consented to contact regarding participation in AT-HOME PD. As of February 15, 2019, 109 individuals have provided eConsent and 70 have completed the baseline visit. There are 75 participants enrolled in Fox Insight and 61 in mPower. A total of 1611 smartphone-based motor tasks (mean 26.41/person) have been completed thus far.

**Conclusions:** Enrollment in AT-HOME PD has successfully been initiated. The study is poised to investigate novel tele-health metrics of PD progression and assess the feasibility of their use in future clinical trials.

## P 082

### Preliminary evidence of CuATSM treatment benefit in Parkinson's disease

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**Background:** A phase 1 study of CuATSM in Parkinson's disease (PD) was initiated based on (1) evidence of decreased copper in the PD substantia nigra (SN) [1]; (2) PET imaging studies showing CuATSM delivers copper selectively to SN in patients with PD [2]; and (3) demonstration that CuATSM treatment was therapeutic in multiple mouse models of PD [3].

**Objectives:** Evaluate safety and tolerability of CuATSM following repeated daily dosing to establish a recommended dose (RD) for further studies. Additionally, obtain preliminary evidence of treatment-related changes in disease severity by UPDRS and quality of life by PDQ-39 after one and six cycles of treatment.

**Methods:** This is a phase 1, multicenter, open-label, dose escalation study in patients with early idiopathic PD. Oral CuATSM is dosed once daily. Dose cohorts (n=6) are evaluated in a 28-day repeated daily dose safety study. At the discretion of the investigator, treatment may be continued for up to six 28-day cycles of treatment. Clinical trial information: NCT03204929.

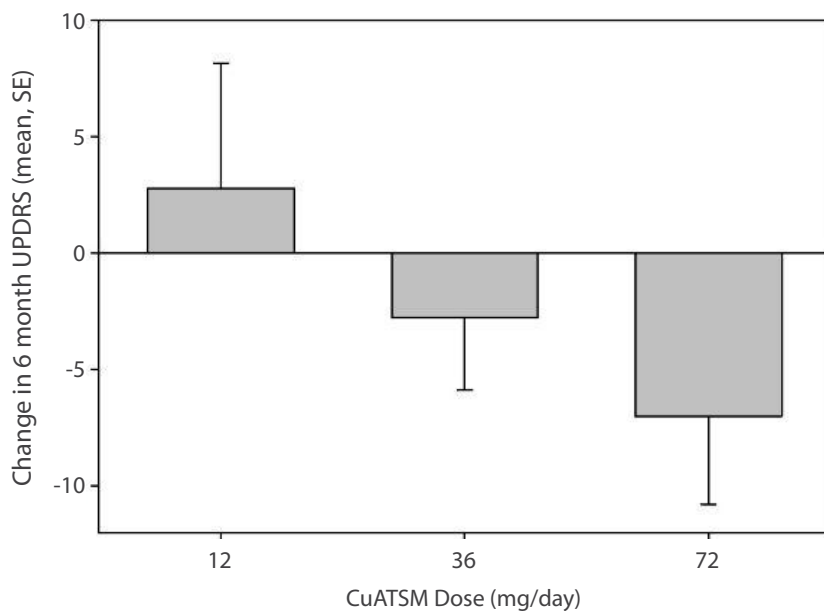
**Results:** 19 Patients were enrolled in three dose cohorts at CuATSM doses of 12, 36 and 72 mg/day. Treatment was well tolerated, with most (13/19) patients completing six 28-day cycles of treatment. Over 24 weeks, dose-related changes in efficacy parameters were observed. At the RD of 72 mg/day, patients

showed improvement in disease severity by UPDRS (mean decrease of 7 points) and improvement in QoL by PDQ-39 (mean decrease of 15 points).

**Conclusions:** Based on treatment tolerance and improvement in UPDRS and PDQ-39 over 24 weeks at RD, further development in a randomized, placebo-controlled trial is justified.

**References:**

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2. Ikawa M, et al, *Nuc Biol Med* 2011; 38:945-951
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[Change in UPDRS Following 6 Months of CuATSM By Dose]



P 083

## Nilotinib's effect on CSF soluble TREM2 (sTREM2) in Parkinson's disease patient's with mild cognitive impairment (MCI)

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**Background:** Nilotinib is a broad-based tyrosine kinase inhibitor with highest affinity to inhibit Abelson (c-Abl) and Discoidin Domain Receptors (DDR1/2). Preclinical evidence indicate that Nilotinib reduces the level of brain alpha-synuclein and attenuates inflammation in models of Parkinson's disease (PD). We previously showed that Nilotinib penetrates the blood-brain-barrier (BBB) and potentially improves clinical outcomes in individuals with PD and Dementia with Lewy Bodies (DLB).

**Methods:** We performed a physiologically-based population pharmacokinetics/pharmacodynamics (pop-PK/PD) study to determine Nilotinib effects in a cohort of 75 PD participants. Participants were randomized (1:1:1:1:1) into 5 groups (n=15) and received open label random single dose (RSD) 150:200:300:400mg Nilotinib versus placebo. Plasma and cerebrospinal fluid (CSF) were collected at 1, 2, 3 and 4 hours after Nilotinib administration.

**Results:** The results show that Nilotinib enters the brain in a dose-independent manner and 200mg Nilotinib increases the level of 3,4- Dihydroxyphenylacetic acid (DOPAC) and Homovanillic Acid (HVA), suggesting alteration of dopamine metabolism. Nilotinib appears to significantly reduce CSF oligomeric:total alpha-synuclein ratio and plasma total alpha-synuclein. Furthermore, Nilotinib significantly increases the CSF level of triggering receptors on myeloid cells (TREM)-2, suggesting an anti-inflammatory effect.

**Conclusions:** Taken together, 200 mg Nilotinib appears to be an optimal single dose that concurrently reduces inflammation and engages surrogate disease biomarkers including dopamine metabolism and alpha-synuclein.

P 084

## Motor responses to apomorphine sublingual film compared with levodopa in patients with Parkinson's disease and "OFF" episodes: Post hoc analysis from a phase 3 study

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**Objectives:** To compare time to onset and magnitude of motor improvement following administration of apomorphine sublingual film (APL-130277; APL) vs levodopa in patients with Parkinson's disease (PD) and "OFF" episodes.

**Methods:** Adult patients with PD and "OFF" episodes receiving levodopa were enrolled into this Phase 3 trial. At screening, patients in a clinically defined "OFF" state were observed for a FULL "ON" response following their normal morning levodopa dose. During open-label titration, patients received 10-35 mg of

APL in 5-mg increments/day until a FULL "ON" response was achieved without intolerable side effects. In this post hoc analysis, motor responses following open-label APL and levodopa administration (n=109) were compared by descriptive statistics using the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III score assessed predose, and 15, 30, 45, 60, and 90 minutes postdose.

**Results:** One hundred nine and 108 patients treated with APL and levodopa, respectively, were analyzed. Predose MDS-UPDRS Part III scores were comparable at screening and titration (43.5 vs 43.1). The magnitude of motor response with APL was ~2-fold higher than with levodopa (-12.6 vs -6.0) at 15 minutes postdose and the observed mean response to APL was greater through 45 minutes postdose. Peak response to APL occurred earlier (45 minutes) than with levodopa (90 minutes), and the magnitude of peak responses was comparable (-26.1 vs -27.9). Responder (defined as a  $\geq 30\%$  decrease in MDS-UPDRS Part III score from predose) rates were 43% vs 18% at 15 minutes and 93% vs 50% at 30 minutes for APL and levodopa, respectively.

**Conclusions:** APL was associated with an earlier onset of motor improvement and earlier peak response vs levodopa in patients with PD and "OFF" episodes. Responder rates were also higher with APL while the magnitude of peak response was similar between APL and levodopa.

## P 085

### A 2-year observation of an excessive daytime sleepiness after subthalamic deep brain stimulation in patients with Parkinson's disease

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**Objectives:** Subthalamic nucleus deep brain stimulation (STN DBS) has a positive effect on overall sleep quality, but its effect on wake functions are controversial. We aimed to assess the longitudinal changes of the quality of sleep and EDS in Parkinson's disease (PD) patients undergoing STN DBS and identify which factors are highly associated with the presence of EDS before and after STN DBS.

**Methods:** A total of 45 PD patients who underwent bilateral STN DBS between July 2011 and October 2015 were recruited. We evaluated subjective sleep quality assessed by Parkinson's Disease Sleep Scale (PDSS) and EDS using Epworth Sleepiness Scale (ESS) preoperatively and 6months, 1 year, and 2 years postoperatively. A cut-off ESS score of  $\geq 11$  was applied.

**Results:** There is a significant improvement in PDSS, and a noticeable change occurs immediately after the surgery. After DBS, the number of patients with persistent EDS gradually decreased, but new patients with worsening of EDS were developed. Consequently, there seemed to be no significant change in the prevalence of EDS before and after DBS. At baseline, there was no significant difference between the patients with and without EDS in the demographic or clinical variables, as well as no meaningful risk factors associ-

ated with EDS. Postoperative worsening EDS was more correlated with an increase of dopamine agonist dose than the severity of PD. Baseline ESS score is highly correlated with EDS at 6 months postoperatively, and use of dopamine agonist is a main risk factor for EDS 1 and 2 years after DBS.

**Conclusions:** Bilateral STN DBS improves the subjective sleep quality, but EDS may improve or worsen. In the long term after surgery, the increase in dose of dopaminergic agonists is thought to have the greatest effect on EDS, and the disease progression might also be partially affected.

**P 087**

### **Efficacy, durability and safety of amprelosetine, a norepinephrine reuptake inhibitor, given once daily to treat neurogenic orthostatic hypotension (nOH) in subjects with primary autonomic failure**

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**Background:** nOH is due to failure of the autonomic nervous system to adequately increase synaptic norepinephrine to maintain upright blood pressure (BP). Norepinephrine reuptake inhibitor (NRI) could augment local synaptic concentrations of tonically released NE, at the vascular sympathetic neuroeffector junction, resulting in increased BP and reduced symptoms of orthostatic hypotension. Amprelosetine (TD-9855) is a novel NRI being investigated for the treatment of subjects with symptomatic nOH.

**Methods:** This was a Phase 2 multicenter, single and multiple-dose study of subjects with nOH. After a single-dose escalation phase, responders were enrolled in an open-label phase, treated with amprelosetine (3 to 20 mg) taken orally once daily for up to 20 weeks, and followed for 4 weeks thereafter. The primary endpoint was the improvement from baseline in the validated symptom questionnaire OHSA#1 on Day 29.

**Results:** 21 subjects were enrolled in the open-label phase (mean age 64 years; 57% MSA). Of these, 16 (76%) completed the Day 29 assessment. The mean [SD] improvement from baseline in OHSA#1 was 2.4 [4.5] in all subjects and 3.8 [3.1] in symptomatic subjects (OSHA#1 >4 at baseline). OHSA and OHDAS composite scores improved by 1.0 (2.8) and 1.1 (2.9), respectively. The mean improvement in standing systolic BP was 7 mmHg. The most frequently reported AEs were urinary tract infection (24%), hypertension (19%), and headache (14%). Two subjects (10%) discontinued treatment due to AE and 5 (24%) reported SAEs, none considered related to the study medication.

**Conclusions:** In subjects with nOH, amprelosetine demonstrated clinically meaningful improvements in OHSA#1, OHSA and OHDAS composite scores at Week 4. The improvement in OHSA#1 was maintained through Week 20, with a regression to baseline levels during the 4 week withdrawal phase. These symptomatic improvements were associated with an increase in standing systolic BP. Amprelosetine was generally well-tolerated.

P 089

## The long-term effect of bilateral STN-DBS on non-motor symptoms in Parkinson's disease: A prospective, observational study

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Bilateral stimulation of the subthalamic nucleus (STN-DBS) improves both motor and non-motor symptoms (NMS) in PD patients. In addition to the short-term improvement of NMS, several studies have shown beneficial effects of up to 24 months post STN-DBS on NMS in PD.

We conducted a three-year follow-up, prospective, observational study on the effect of STN-DBS on a plethora of NMS in PD. Thirty three consecutive patients (13 females, mean age  $62.3 \pm 7.4$  years, mean disease duration at operation  $13.6 \pm 4.4$  years) were assessed preoperatively and then at 6 months, one, two and three years after the operation. They were assessed by Non-Motor Symptoms Scale (NMSS), Montreal Cognitive Assessment (MoCA, Beck Depression Inventory (BDI), Hamilton Anxiety Scale (HAS), Starkstein Apathy Scale (SAS), and Parkinson's Disease Sleep Scale (PDSS-2). Quality of life was assessed by the Parkinson's Disease Questionnaire 39 (PDQ39).

Total Non-Motor Symptoms Scale (NMSS) score improved, as did depression, anxiety, sleep, and quality of life scores. There was a trend towards improvement of apathy. As expected, the general cognitive abilities did not change.

We may conclude that the improvement of NMS after STN-DBS is sustained for a longer time, an important fact that has to be taken into account in the pre-surgical decision process.

P 090

## Long-term safety and tolerability of apomorphine sublingual film in patients with Parkinson's disease and "OFF" episodes

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**Objectives:** To evaluate the long-term safety and tolerability of apomorphine sublingual film (APL-130277; APL) for the acute, intermittent treatment of "OFF" episodes in a pooled analysis of patients with Parkinson's disease (PD).

**Methods:** Adult levodopa-responsive patients with PD and "OFF" episodes exposed to APL doses of 10-35 mg for  $\geq 6$  months were included in this pooled safety analysis. Treatment-emergent adverse events (TEAEs) were reported using descriptive statistics.

**Results:** One hundred patients were exposed to APL for  $\geq 6$  months (across both titration and maintenance treatment phases). Median exposure was 7.3 months (range, 6-13 months), with a total of 59.8 patient-years of exposure. Eighty-four percent of patients were exposed to APL for  $\geq 6$  to  $< 9$  months, 14% for  $\geq 9$  to  $< 12$  months, and 2% for  $\geq 12$  months. Among these 100 patients, TEAEs were reported in 90% of patients. Serious TEAEs occurred in only 6% of patients and 5% discontinued treatment due to a TEAE. No TEAEs resulted in death. The most common TEAEs were nausea (24%), oral mucosal erythema (12%), fall (12%), somnolence (10%), dizziness (9%), and yawning (9%). Lower rates of TEAEs of interest were reported for orthostatic hypotension (6%), dyskinesia (5%), contusion (5%), and mouth ulceration (5%); less common TEAEs of interest included syncope (2%), hallucinations (2%), and impulse control disorders (1%).

**Conclusions:** No new or unexpected findings were identified in this long-term safety analysis of apomorphine administered as a sublingual film in patients with PD and "OFF" episodes. Consistent with shorter-term studies, APL was found to be generally well tolerated.

#### P 091

### **Mental rotation task test (MRT) scores are correlated to higher infixed Parkinson's disease rating scores (UPDRS) in early onset idiopathic Parkinson's disease**

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Parkinson's disease (PD) begins with unilateral symptoms (H&Y Stage I). Approximately 20% of PD patients exhibit disease symptoms between the ages of 40-60 years and are classified as early-onset Parkinson's disease (EOPD). Monitoring disease progression is critical in EOPD patients as they are at increased risk to develop motor complications.

We selected a battery of hemispheric-weighted neuropsychological tests to determine if one or more of these subclinical cognitive deficits are predictors of disease progression. Forty-four EOPD Stage I subjects have been enrolled in this study. Subjects were divided into the following subgroups: male right-onset EOPD (MRPD), male left-onset EOPD (MLPD), female right-onset EOPD (FRPD) and female left-onset EOPD (FLPD). Subjects were screened using the Edinburgh Handedness Inventory, Beck Depression Inventory-II, and the Montreal Cognitive Assessment (MoCA). Our test battery consisted of the Delis-Kaplan Verbal Fluency Test, the MRT, the Delis-Kaplan Design Fluency test, the Wechsler Memory Scale Visual Reproduction I and II, the California Verbal Learning Test (CVLT-II), the Woodcock Johnson Picture Vocabulary Test and a mirror tracing task. MRT was significantly impaired compared to age-matched published controls and the right-sided EOPD subjects performing significantly better than the left-onset EOPD subjects ( $p=0.0203$ ) in this test.

As expected, male subjects significantly outperformed female subjects ( $p=0.0149$ ). MRPD subjects significantly scored better than MLPD subject ( $p=0.0311$ ). Despite lower scores, there was separation between FRPD and FLPD subjects that approached statistical significance ( $p=0.0847$ ). Total UPDRS scores in left-onset EOPD men and women were larger than right-onset subjects.

Our finding suggests that there are specific visual-spatial deficits, as determined by the MRT, in stage I EOPD subjects with no clinical bedside evidence of cognitive decline or depression. This supports the notion that visuospatial deficits may account for worse PD prognosis in left-onset EOPD subjects and MRT could be a putative biomarker for disease progression.

## P 092

### Once-daily opicapone Increases ON-time in patients with Parkinson's disease: Results from two phase 3 studies

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**Objectives:** To evaluate changes in ON-time with once-daily opicapone in Parkinson's disease (PD). Catechol-O-methyltransferase (COMT) inhibitors were developed to prolong the clinical effect of levodopa. Opicapone, a highly selective COMT inhibitor, is approved in Europe and under development in the U.S. as an adjunct to levodopa in adults with PD and motor fluctuations. The efficacy of opicapone has been evaluated in two international Phase 3 studies (BIPARK-1 [NCT01568073], BIPARK-2 [NCT01227655]).

**Methods:** Participants received double-blind (DB) treatment with opicapone (5mg [BIPARK-1 only], 25mg, 50mg), entacapone 200mg (BIPARK-1 only), or placebo for 14-15 weeks added to levodopa. Participants completing DB treatment were eligible to enroll in the 1-year open-label (OL) extension of each study. Efficacy analyses included mean changes from baseline in absolute ON-time without troublesome dyskinesia (defined as no dyskinesia or non-troublesome dyskinesia). Incidence of dyskinesia as a treatment-emergent adverse event (TEAE) is presented.

**Results:** In BIPARK-1 (opicapone at 5mg=119, 25mg=116, 50mg=115; entacapone=120; placebo=120), a significant increase from baseline to Week 14/15 in absolute ON-time without troublesome dyskinesia was found for opicapone 50mg versus placebo (least-squares mean change [ $\pm$ standard error], hours): 50mg,  $1.9\pm 0.2$ ; placebo,  $0.9\pm 0.2$ ;  $P=0.002$ . Similar results arose from BIPARK-2 (25mg=125, 50mg=147, placebo=135): 50mg,  $1.7\pm 0.3$ ; placebo,  $0.9\pm 0.3$ ;  $P=0.025$ . Improvements in ON-time without troublesome dyskinesia were sustained in participants enrolled in OL extension studies, with mean changes from DB baseline to OL endpoint ( $\pm$ standard deviation) of  $2.0\pm 2.6$  hours for BIPARK-1 (N=494) and  $1.8\pm 3.2$  hours for BIPARK-2 (N=339). In the pooled DB safety population (opicapone=631, placebo=257), a TEAE of dyskinesia was reported in 17.4% of all opicapone-treated participants (versus 6.2% for placebo). Few participants had dyskinesia leading to discontinuation (opicapone, 1.9%; placebo, 0.4%) or serious dyskinesia (opicapone, 0.3%, placebo, 0%).

**Conclusions:** Once-daily opicapone increased ON-time without troublesome dyskinesia in PD patients with motor fluctuations with improvement sustained up to 1 year.

P 093

## Exploring transcranial alternative current (tAC) stimulation the neglected player in Parkinson's disease: Pilot study of cognitive modulation effects of Alpha Stim® in normal control subjects

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**Introduction:** Recently, transcranial alternating current stimulation: tACS, via interacting with the endogenous oscillating activity, has drawn emerging interest in PD. A pioneering clinical study in PD showing tACS applied over the motor cortex, suppressed PD resting tremor by inducing phase cancellation of rhythm. The Cranial electrotherapy stimulation: CES device: Alpha-Stim® (Electromedical Products International (Epi,TX USA )consists of transmitting pulsed, alternating micro-current (100-500 µA) to the cranial region through electrodes applied to the earlobes capable of modulating brain wave oscillations and brain-behavior functions.

**Objective:** The objective of our dose-finding study is to examine:

- 1) the safety and tolerability;
- 2) cognitive effects of applying Alpha-Stim® over a week-period to normal healthy control subjects.

**Method:** We recruited healthy subjects with no neurological and serious medical disorders from Dalian province, China in 2012 . Our protocol entailed the subjects who signed informed consent to receive daily 30-minute Alpha-Stim® sessions for 7 days. The subjects positioned the Alpha-Stim® to bilateral electrodes at the individualized frequency level (mean 0.5 Hz) for which they experienced "floating sensation". The subjects were required to monitor for adverse events and to rate the changes using self-reported symptom checklist adapted from CGI(Clinical Global Impression)-improvement score, prior to, and during the Alpha-Stim® administration.

**Results:** 9 subjects: age range 15-50 years, male/female 6/3 participated and completed the study. Both the student sub- group:n=6, and the adult sub-group:n=3, reported onset of action within 5 minutes and found highly favorable ratings in cognitive domains of concentration and attention spans, processing speed ,cognitive flexibility, problem solving and logical reasoning, as well as sustained improvement in retention and retrieval of data, compared with baseline. Both groups experienced reduced performance anxiety, sustained positive mood states, and improved sleep quality. No adverse events were noted.

**Conclusion:** We will corroborate neural-plasticity-mediated cognitive and behavioral effects of Alpha-Stim® in designing RCT in PD.

P 094

## Exploring Prolyl-Lecuyyl-glycinamide(PLG) and PLG Peptidomimetic: PAOPA [ 3(R)- [(2(S)pyrrolidinylcarbonyl)amino]-2-oxo-1 pyrrolidineacetamide] as a prototypal dopamine receptor: D-2/D-4 allosteric modulator as novel drug lead for Parkinson's disease

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**Introduction:** While L-DOPA provides symptomatic relief to Parkinson's disease (PD) motor symptoms, none of the currently approved PD drugs modify the course of PD and prevent PD complications: dyskinesia, psychosis and dementia. Discovery of allosteric modulators of G-Protein-coupled receptors(GPCR) may open a new vista in PD therapeutics. Our research group in targeting dopamine receptors (DA) through GPCR pathway, has synthesized potent analogue of the tripeptide, L-Prolyl-L-leucyl-glycinamide (PLG): PAOPA.

**Objective:** The objective of our series of study is 1) to characterize the molecular interaction of PAOPA with DA affinity states ; 2) to examine the efficacy of PAOPA in translation models of PD; 3) to evaluate the effects of PAOPA in dyskinesia model; 4) to investigate the anti-psychotic effect of PAOPA in psychosis model.

**Result:** In the neuroblastoma SH-SY5Y cells stably transfected with respective cDNAs PLG and PAOPA increased the population and affinity of the high-affinity form of the D2L receptor and attenuated guanosine 5'-(beta,gamma-imido)-triphosphate-induced inhibition of high-affinity agonist binding sites for the DA D2L receptor; and PLG requires the D2L receptor/G protein complex to increase agonist binding. 2) PAOPA was 100x fold potent than PLG in two PD models: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesioning model with C57 BL/6 mice and in the 6-hydroxydopamine (6-OHDA)-lesioned rotational behavior rodent model. 3) In the vacuous chewing movements (VCM) rat model of tardive dyskinesia (TD) PAOPA was 100-fold more potent than PLG in attenuating the dyskinetic movements . 4) PAOPA reversed aberrant behavior in the rodent model of amphetamine sensitization psychosis

**Conclusion:** Our results suggest that PLG and PAOPA modulate DA D2S, D2L, and D4 receptors through G-protein coupling PAOPA behaves as the prime PAM(Positive allosteric modulator) and NAM (Negative allosteric modulator)-DA receptor. PAOPA in exhibiting anti-Parkinsonian, anti-dyskinetic and anti-psychotic triad properties, merits fast-tracking to the PD clinical trial arena as promising innovative disease-modifying PD drug.



P 095

## **Safety and tolerability of apomorphine sublingual film in patients with parkinson's disease and "OFF" episodes: A pooled analysis of adverse events of special interest**

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**Objectives:** To describe reported prespecified adverse events of special interest (AESIs) from a pooled analysis of 4 studies of apomorphine sublingual film (APL-130277; APL) in patients with Parkinson's disease (PD) and "OFF" episodes.

**Methods:** All adult levodopa-responsive patients with PD and "OFF" episodes exposed to  $\geq 1$  dose of APL (10-60 mg/dose) were included. AEs were reported using descriptive statistics. For AESI categories, time to onset and duration of first occurrence were assessed using Kaplan-Meier analysis.

**Results:** Among the 408 and 285 unique patients in the pooled titration and maintenance phases, 36% and 50%, respectively, reported AESIs. The most frequent AESI by category ( $\geq 5\%$ ) and preferred terms (PT) within each category during titration and maintenance phases respectively, were: hypotension/orthostatic hypotension (15%, 9% [PT, dizziness: 11%, 6%]); daytime sudden onset of sleep (12%, 10% [PT, somnolence: 11%, 7%]); stomatitis, oral ulcers, and oral irritation or allergic/sensitivity response to the formulation (10%, 29% [PT, oral mucosal erythema: 4%, 5%; lip swelling: 0%, 5%]); and falls and injuries (5%, 12% [PT, fall: 2%, 5%]). The following AESI categories were infrequent ( $\leq 4\%$ ) or did not occur: dyskinesias; syncope; impulse control disorders; hallucinations and psychotic behaviors; and acute coronary syndrome, myocardial infarction, and angina. No AESI during titration was considered serious; 4 patients had 5 serious AESIs during maintenance (hypotension and syncope, fall, spinal compression fracture, and femoral neck fracture). Regarding oral mucosal tolerability, probabilities of the first event occurring by day 50, 100, 150, and 200 were 19%, 33%, 36%, and 40%, respectively. Probability of first oral event lasting  $< 50$  and  $< 100$  days was 92% and 97%, respectively.

**Conclusions:** APL was well tolerated and observed AESIs were generally mild to moderate. Findings were consistent with known effects of apomorphine and dopamine agonists, except for local site reactions associated with sublingual administration.

P 096

## Dopa-resistant apathy in Parkinson's disease

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**Background:** Some motor and non-motor symptoms associated with PD do not seem to respond well to levodopa and appear to be resistant to such dopaminergic treatment with disease progression. Thus, PD patients often have both levodopa-responsive and levodopa-resistant symptoms or signs.

**Objectives:** This study aims to explore the clinical differences between patients with dopa-responsive apathy and dopa-resistant apathy in a cohort of Chinese PD population.

**Methods:** A total of 85 newly diagnosed apathic PD patients who had completed a 1-year follow-up visit from West China Hospital of Sichuan University were analyzed. The symptom of apathy was assessed by the Lille Apathy Rating Scale (LARS) both at baseline and follow-up. At the follow-up visit, all patients had received dopaminergic treatment more than 6 months. Each subject was categorized as dopa-responsive apathy or dopa-resistant apathy based on the change of LARS score from baseline to follow-up.

**Results:** This study included 50 male and 35 female patients, with mean age of  $59.8 \pm 12.3$  years and mean duration of  $2.6 \pm 1.6$  years. Fifty patients were classified as dopa-resistant apathy (58.8%). Patients with dopa-resistant apathy showed significantly higher education, lower age, higher Montreal Cognitive Assessment (MoCA) language and abstraction subscores, and higher Frontal Battery Assessment (FAB) similarity subscore ( $P < 0.05$ ) at baseline than those with dopa-responsive apathy. The LARS score and its subscores were significantly lower in patients with dopa-resistant apathy than those in patients with dopa-responsive apathy at baseline ( $P < 0.05$ ). The forward binary logistic regression model indicated that higher education ( $OR=1.175$ ,  $95\%CI=1.021-1.351$ ,  $P=0.025$ ), younger age ( $OR=0.933$ ,  $95\%CI=0.884-0.985$ ,  $P=0.012$ ), and higher similarity score ( $OR=4.248$ ,  $95\%CI=1.392-12.965$ ,  $P=0.011$ ) were associated with dopa-resistant apathy in PD.

**Conclusions:** Our study reveals the clinical discrepancies between dopa-responsive apathy and dopa-resistant apathy in PD, which probably suggest that the underlying pathophysiology between the two groups is different

P 097

## Canadian patient perspective on the burden of Parkinson's disease and 'OFF' episodes

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**Objectives:** To describe burden of Parkinson's Disease (PD) and 'OFF' episodes from the perspective of PD patients in Canada.

**Methods:** This mixed methods research comprised of an online survey and telephone interviews with PD patients. Surveys were conducted July-August 2018 among 50 patients, and 30-45-minute semi-structured telephone interviews were conducted June-September 2018 with 16 patients across Canada

(Quebec, Ontario, Alberta, British Columbia (BC)). Inclusion criteria include age  $\geq 20$  years old, physician-diagnosed with PD, currently taking levodopa/carbidopa, had a dosing/frequency change in past year or taking PD medication (e.g., dopamine agonist, COMT inhibitor) in addition to levodopa/carbidopa, and reported experiencing 'OFF' episodes.

**Results:** Among surveyed patients (N=50), mean age was 56 and most were male (64%). Almost half (46%) were retired and 38% worked full-time. Majority (64%) experienced 'OFF' episodes daily. 'OFF' episodes most commonly occurred in the morning (44%) or unexpectedly (44%). Three-quarters (74%) reported that PD symptoms had a somewhat to very extensive impact on their quality of life (QoL) or general well-being. From interviews, patients described many challenges of PD and 'OFF' episodes, "About twice a day, for maybe half an hour, I shake; my legs tremble, my arms tremble, the whole of my body moves, and people notice." Majority (62%) required support (e.g., caregiver) for their daily activities. Among patients with a caregiver (n=31), 75% reported that 'OFF' episodes had a somewhat to very extensive impact to their caregivers, and 61% reported that their caregiver often had to take time off work or other responsibilities to help treat 'OFF' episodes.

**Conclusions:** PD and 'OFF' episodes greatly impact QoL and daily activities of patients. Furthermore, patients perceive this impact to extend to their caregivers as well. Thus, optimal management of PD and 'OFF' episodes may provide value to both PD patients and their caregivers.

## P 098

### Canadian caregiver perspective on the burden of Parkinson's disease and 'OFF' episodes

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**Objectives:** To describe burden of Parkinson's Disease (PD) and 'OFF' episodes from the perspective of caregivers of PD patients in Canada.

**Methods:** This mixed methods research comprised of an online survey and telephone interviews with caregivers of PD patients. Surveys were conducted July-August 2018 among 50 caregivers, and 30-45-minute semi-structured telephone interviews were conducted June-September 2018 with 15 caregivers across Canada (Quebec, Ontario, Alberta, British Columbia (BC)). For the patient of caregiver, inclusion criteria include age  $\geq 20$  years old, physician-diagnosed with PD, currently taking levodopa/carbidopa, had a dosing/frequency change in past year or taking PD medication (e.g., dopamine agonist, COMT inhibitor) in addition to levodopa/carbidopa, and reported experiencing 'OFF' episodes. The caregiver also had to actively participate in patient's medical treatment decisions and discussions.

**Results:** Among surveyed caregivers (N=50), mean age was 55 and most were female (58%). Forty-two percent were retired and 40% worked full-time. Caregivers provided a range of support, including attending doctor appointments (96%), participating in treatment decisions/discussions (94%), and supporting in other ways (e.g., driving to appointments) (98%). About a quarter (26%) reported that they had to take time off work or other responsibilities to help treat 'OFF' episodes. In addition, among those who care for patients on 'OFF' episode medication, 58% reported that they made extra trips to give 'OFF' episode

medication. From interviews, caregivers described challenges of PD for the patient and themselves. For example, "I won't go out for a long time and leave him just because he does fall sometimes. I end up having to do more because he is slow at getting things done."

**Conclusions:** PD and 'OFF' episodes greatly impact QoL and daily activities of both patients and their caregivers. Thus, optimal management of PD and 'OFF' episodes may provide value to both PD patients and their caregivers.

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## Self-reported subtype change in Parkinson's disease: A retrospective study

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**Objectives:** To determine the prevalence of motor subtype change and its clinical correlates.

**Methods:** PD cases were retrieved from movement disorders clinic database. Initial subtype was registered as reported by the patient: tremor-dominant (TD), Non-Tremor-Dominant (Non-TD) including rigidity/bradykinesia(R/B), postural instability/gait disorder (PIGD). Actual subtype was assessed with MDS-UPDRS part III: TD, and Non-TD (sum of PIGD, and indeterminate-IND). Motor subtype change was registered. Variables were compared between groups.

**Results:** We included 105 cases, male (67.6%; n= 71), mean age 60.3±11.9 years; age at onset 54.7±12.8, and disease duration 7.2±5.4 years; Hoehn & Yahr (H&Y) 2.4±0.9. TD was the most frequent initial subtype (62.9%; n= 66), yet the most common actual subtype was PIGD (56.2%; n= 59).

Change of motor subtype was recorded in 58 patients (55%), the most common from Tremor-Dominant to Non-Tremor-Dominant (57%, n= 34). Significantly higher mean H&Y stages were found in the "Tremor-Dominant to Non-Tremor-Dominant" group than in vice-versa group (2.6±1.0, vs 2.0±0.6; p= 0.008); the most prevalent subtype in the No-change group was Non-Tremor-Dominant (PIGD 64%, IND 26%). Without significant difference in age at onset or disease duration. Details are depicted in table 1.

**Conclusions:** More severe disease was found in those who change from Tremor-Dominant to Non-Tremor-Dominant, and in those who remained unchanged, without difference in age at onset or disease duration, which suggests change isn't simply progression of disease.

	No change (n= 47)	TD to Non-TD (n= 34)	Non-TD to TD (n= 24)	
Age at onset	55.1 ± 11.9	52.9 ± 13.9	56.7 ± 12.9	0.573
Duration	6.0 (1.0 - 20.0)	6.0 (1.0 - 21.0)	4.0 (1.0 - 23.0)	0.351
Hoehn & Yahr	2.5 ± 0.9	2.6 ± 1.0	2.0 ± 0.6	0.008

«PIGD, Postural Instability/Gait Disorder. \*Chi square, t test or Mann-Whitney U where appropriate.»

[Table 1. Comparison between subtype change groups.]

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# Cognitive correlates of quality of life in patients with Parkinson's disease

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**Objectives:** To determine the correlation between domain-specific cognitive assessment and quality of life in patients with Parkinson's disease (PD).

**Methods:** Cases of PD patients were selected from the outpatient neurology clinic database, if they had complete scales for cognitive assessment with Montreal Cognitive Assessment (MoCA), and quality of life with the PD 8-item Questionnaire (PDQ8). Non-parametric correlations were sought between total and domain-specific scores of both MoCA and PDQ8, then stepwise linear regression models were used to determine predictive variables of quality of life.

**Results:** 78 cases were found for analysis, of which 53 (68%) were male, had an average age 60.5±11.6 years; mean education years 10.6±4.9; disease duration 6.6±5.4 years; mean age of onset of 55.5±12.2 years; and mean Hoehn & Yahr 2.3±0.8. Cognitive assessment revealed a mean MoCA score of 24.0±4.0, only 12(15%) had MoCA < 21. There was a positive correlation between language and Parkinson's disease progress (Hoehn & Yahr) (r=0.21, p=.023), and there was a negative correlation between memory delay and depression (r=-0.54, p=.033). Stepwise linear regression yielded two models, with Hoehn & Yahr stage and Identification domain remaining as significantly predictive variables for PDQ8 score (Table 1).

**Conclusions:** In patients with Parkinson's disease, quality of life is correlated with domain-specific rather than global cognitive impairment. With worse scores in the Identification domain and a more severe Hoehn & Yahr stage being predictive variables for worse quality of life scores.

	Std. Error	β	t	OR	[95% CI]	P
[Model 1]						
Identification Domain	1.328	-0.262	-2.268	-3.0	[-5.7 to -0.4]	0.026
[Model 2]						
Identification Domain	1.285	-0.299	-2.681	-3.4	[-6.0 to -0.9]	0.009
[Model 2] Hoehn & Yahr	0.867	0.294	2.633	2.3	[0.6 to 4.0]	0.010

Dependent Variable: PDQ8. Variables Included: MoCA total and domains (visuospatial, attention, language, abstraction, delayed recall, orientation); age; years of education, disease duration, age at disease onset, Hoehn & Yahr stage, MDS-UPDRS III.

[Stepwise linear regression model]

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## Tele park: Evaluation of the appropriation of a digitally guided self-rehabilitation device for patients with Parkinson's disease and their professional helpers on a health territory

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**Objectives:** The challenge of neurological rehabilitation management is the continuation of long-term physical activity. The BYM digital movement training tool is in line with this trend: to encourage daily self-exercise.

The main objective of this study is to evaluate the appropriation of BYM by patients and their liberal physiotherapists in a health area in people with Parkinson's disease.

**Methods:** This prospective, observational, open study included liberal physiotherapists and their Parkinsonian patients with balance and walking disorders.

The main criterion is an acceptability questionnaire for new UTAUT - Unified Theory of Acceptance and Use of Technology model technologies with a high predictive power for future use of a technology. Scores based on the determinants of UTAUT are assessed at 2 months and 1 year at the inclusion of professionals and patients.

**Results:** 71 liberal physiotherapists were contacted and 11 consented to participate, 27 patients were included. Measured on a 5-point Likert scale[0-4], the subscores of the determinants of intention to use support inclusion for both professionals and patients. The determinants of use are utility (expected performance=3.1), accessibility (expected effort=3.3) and playfulness (gaming: 3.4). The environment also seems favourable (social influence: 3.4). At 2 months out of the first 14 patients, the intention to use decreases in relation to an expected efficacy not achieved.

**Conclusions:** The solution benefits from a positive a priori for users but this good acceptability is confronted with a lower acceptance rate of 2 months in relation to the expected benefit not achieved. Nevertheless, the implementation of the tool is possible within the liberal cabinets allowing to bring one more tool to the rehab professionals

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## Prospective observational study to follow up a cohort of Parkinson's patients during a 4-week rehabilitation ambulatory care

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**Objectives:** To evaluate the effectiveness of a 4-week program in a rehabilitation centre for physical activities and exercise on balance, walking and upper limb bradykinesia in Parkinson's patients

**Methods:** Observational, prospective, monocentric study, cohort follow-up of Parkinson's patients or related patients over 2 years consisting of the implementation of a rehabilitation program in groups of 4 to 6 people for 4 weeks in ON at a rate of 3 days/week based on reconditioning to effort, global and analytical muscle strengthening of extensors, work on balance and double task, setting in ecological situations and motor imaging work.

**Results:** 113 patients participated, average age was 67.9 years (min 44 years, max 83 years), average diagnostic time 8.4 years (SD 5.2), Hoehn and Yahr 2.6 (SD 0.6), UPDRS II+III 24.8 (SD 9.4). Statistically significant differences were observed across all clinical balance and walking tests (Time Up and Go  $p=0.04$ , Time to test 10m at comfortable speed  $p=0.02$  and fast  $p=0.03$ , distance covered in 2 minutes  $p=0.0004$  and in 6 minutes  $p<0.0001$ ). The results are also statistically significant on global and fine grips outside the Nine Hole Peg test on the left.

**Conclusions:** This study in a rehabilitation centre therefore shows not only the feasibility of setting up a standardised group rehabilitation programme but also its immediate effectiveness. Work is still in progress to offer patients innovative self-rehabilitation tools in order to hope for the persistence of a long-term benefit by maintaining physical activity adapted to these pathologies in order to maintain the best possible autonomy and quality of life for as long as possible.

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## The anti-dyskinetic effect of the clinically-available mGluR<sub>2</sub> positive allosteric modulator AZD-8529 in the 6-OHDA-lesioned rat

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**Objectives:** To determine the effect of the metabotropic glutamate receptor 2 (mGluR<sub>2</sub>) positive allosteric modulator (PAM) AZD-8529, on L-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesia in the 6-hydroxydopamine (6-OHDA)-lesioned rat model of Parkinson's disease.

**Methods:** Following 6-OHDA-lesion of the right medial forebrain bundle to render rats hemi-parkinsonian, animals underwent the cylinder test to assess the degree of parkinsonism. Severely parkinsonian rats were selected and primed daily with L-DOPA to induce stable and reproducible abnormal involuntary

movements (AIMs). On experimental days, AZD-8529 (0.1, 0.3, 1 mg/kg) or vehicle was administered in combination with L-DOPA. The duration and amplitude of axial, limbs and orolingual (ALO) AIMs severity was evaluated. Following a 3-day washout period, the effect of AZD-8529 on L-DOPA anti-parkinsonian action was assessed by the cylinder test.

**Results:** We found that administration of AZD-8529 (0.1, 0.3 and 1 mg/kg) with L-DOPA significantly decreased the duration of ALO AIMs by 9%, 9%, and 15%, respectively (all  $P < 0.05$ ) when compared to L-DOPA/vehicle. In contrast, administration of AZD-8529 in combination with L-DOPA did not significantly decrease the amplitude of ALO AIMs. AZD-8529 administration did not interfere with the anti-parkinsonian action of L-DOPA.

**Conclusions:** Our results suggest that mGluR<sub>2</sub> activation may be a promising treatment strategy to alleviate L-DOPA-induced dyskinesia, without hindering with therapeutic benefits of L-DOPA.

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### Efficacy, safety, and tolerability of supratherapeutic doses of apomorphine sublingual film for the treatment of "OFF" episodes in patients with Parkinson's disease

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**Objectives:** To evaluate efficacy, safety, and tolerability of supratherapeutic doses of apomorphine sublingual film (APL-130277; APL) in patients with Parkinson's disease (PD) and "OFF" episodes.

**Methods:** Patients with PD on stable medications without antiemetics who demonstrated drug withdrawal-induced "OFF" episodes were eligible. Patients received increasing doses of APL (10-60 mg) until a FULL "ON" response was achieved, and then received 2 additional supratherapeutic doses, if tolerated (maximum 60 mg). Differences in efficacy between the lowest dose resulting in a FULL "ON" response (low) and the highest supratherapeutic dose received (high), if different, were explored by comparing changes in Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III scores from predose to 30, 60, and 90 minutes postdose using a Repeated Measurements model. Time to and duration of FULL "ON" were evaluated using Kaplan-Meier analysis.

**Results:** Forty-eight patients received  $\geq 1$  dose of APL (safety population); 35 were evaluable for exploratory efficacy analyses. The dose to FULL "ON" was  $\leq 20$  mg for 79% of patients. Superior mean reduction in MDS-UPDRS Part III scores was observed for high- vs low-dose APL (least squares mean  $\pm$  standard error difference was  $-5.5 \pm 2.47$ ;  $P=0.0325$ ,  $-4.9 \pm 1.63$ ;  $P=0.0052$ , and  $-3.7 \pm 1.50$ ;  $P=0.0190$  at 30, 60, and 90 minutes postdose, respectively). Median time to FULL "ON" (30 minutes), earliest observed time to FULL "ON" (10 minutes), and probability of patients with a FULL "ON" duration of  $\geq 50$  minutes ( $\sim 90\%$ ) were similar



between doses. The most common treatment-emergent adverse events (TEAEs) were nausea (56%), somnolence (25%), vomiting (19%), and dizziness (17%); these were generally transient and mild to moderate in severity. No serious TEAEs or deaths were reported.

**Conclusions:** Administration of APL at doses above those necessary to produce an apparent FULL "ON", without antiemetics, may provide additional benefits in the treatment of "OFF" episodes.

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## **Clinical analysis of Levodopa-induced dyskinesia associated with autophagy dysfunction and the effect of Adenosine A<sub>2A</sub> receptor antagonist**

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**Objectives:** To evaluate the Levodopa induced dyskinesia (LID) in the clinical view point of autophagy and cellular energy dysfunction, and the pharmacological effect of adenosine A<sub>2A</sub> receptor antagonist (Istradefylline; IST) adjunct to L-dopa (IST-Ld).

**Background:** Chronic L-dopa treatment should enhance cAMP dependent pathways activation with phosphorylation (p-), together with cAMP independent non-canonical signaling pathways with activation of m-TORC1. A<sub>2A</sub> R receptor antagonist have the potential to activate MAPK signaling to regulate the cellular energy metabolism and inducing autophagy.

**Methods:** The cohort recruited 62 patients with early to advanced stages of PD as part of open-label trials for five years from 2013 to 2018. Effects of the IST-Ld were prospectively measured with Clinical Global Impression-Global Improvement Scale (CGI-I), and the Unified Parkinson's Disease Rating Scale (UPDRS), and Unified Dyskinesia Rating Scale (UDysRS). The biomarkers of autophagy functions were measured; body weight changes ( $\Delta$ ), levels of neuropeptides such as Insulin-like growth factor I (IGF-I) of the serum, and the ketone body of urine. The levels of p- $\alpha$ -synuclein of plasma (IMR) were measured as biomarkers of dopamine nerve dysfunction of the severe dyskinesia patients. Wilcoxon signed-rank test and binomial logistic regression analysis were used with IBM SPSS statistics version 12.0.

**Results:** The frequency of dyskinesia were; baseline, 26.1%; 36 months, 39.6%, 60 months 40%. The OR with genesis of dyskinesia were; levodopa equivalent daily dose,  $\Delta$ body weight, UPDRS part 3 score, and serum IGF-I ( $p < 0.05$ ).

**Conclusions:** IST-Ld did not promote the genesis of dyskinesia, which may be both the possibility of the L-dopa sparing effect of IST and the suppression of L-dopa induced m-TORC1 with aberrant downscaling of autophagy and energy metabolism.

### **Reference:**

1. N. Kanzato. Branched chain amino acid (BCAA) and cellular metabolism. -alternative therapy for tardive extrapyramidal disorders-. Psychiatry (Seishinka) 2019, 34(1), 1-5.

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## Association between cognitive performance and neuropsychiatric symptoms in patients with Parkinson's disease

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**Objectives:** To determine the correlation between cognitive performance and neuropsychiatric symptoms in patients with Parkinson's disease (PD).

**Methods:** Retrospective study. Consecutive patients with PD, seen at the neurology outpatient clinic were evaluated with the Montreal Cognitive Assessment (MoCA) and with the Scale for Evaluation of Neuropsychiatric Disorders in PD (SEND-PD). To determine association between cognitive performance and neuropsychiatric symptoms, bivariate correlations were determined between domains of beforementioned scales.

**Results:** Seventy-eight patients (53 male and 25 female, mean age  $60.5 \pm 11.6$  years, years with PD  $6.5 \pm 5.3$ , Hoehn & Yahr stage  $2.3 \pm .7$ , scholarship of  $10.6 \pm 4.8$  and MoCA total  $24.1 \pm 4.0$ ) were evaluated; there was a negative correlation between naming and mental fatigue ( $r=-.377$ ,  $p=.001$ ), and between naming and apathy/lack initiative ( $r=-.259$ ,  $p=.022$ ), furthermore there was a negative correlation between delay recall with Hoehn & Yahr stages ( $r=-0.234$ ,  $p=-0.39$ ).

**Conclusions:** The correlation between naming and mental fatigue can be explained by the neural network involved in this task, which is related to the pars triangularis of the left inferior frontal gyrus (Brodmann area 45) required for the retrieval process and knowledge of animals, the increased activity of this area has been found to be related to required effort for cognitive performance. Mental fatigue can be explained by the dopamine deficit [DH1]. The presence of neuropsychiatric symptoms is associated with cognitive deterioration, which negatively impacts the quality of life of patients. The neuropsychological evaluation is essential for the early detection of cognitive and behavioral alterations, in order to implement non-pharmacological therapies.

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## Interim analysis of an open-label study of pimavanserin in patients with comorbid Parkinson's disease and depression

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**Objectives:** Depression occurs in ~50% of Parkinson's disease (PD) patients, increases in severity and duration as the disease progresses, and is associated with increased morbidity. Improvement of depression in PD patients is correlated with reduced physical disability and improved quality of life. We are assessing use of pimavanserin (PIM) for treatment of depression in adults with PD.

**Methods:** A Phase-2, 8-week, open-label, single-arm study is being conducted to evaluate the safety and efficacy of PIM as an adjunct to SSRI/SNRI or as monotherapy in adults with both PD and symptoms of depression (baseline Hamilton Depression Scale [17-items] total score [HAMD-17]  $\geq 15$ ). The primary end-point of the study is change from Baseline to Week 8 in the HAMD-17. Secondary measures included the Clinical Global Impression (CGI) scales (improvement and severity) and Scales of Outcomes in PD-Sleep (SCOPA).

**Results:** Interim results based on the first 27 patients have been evaluated. 55.6% of patients are male and average age is 68.7 years. At baseline, patients had a mean(SE) HAMD-17 of 19.9(0.74). Change from Baseline to Week 8 (least squares mean [LSM] [SE]) in the HAMD-17 was -10.1(1.2) (95% CI:-12.7;-7.5;  $p < 0.001$ ), with significant improvement seen as early as Week 2 (-8.3[1.3]; 95% CI:-11.0;-5.5;  $p < 0.001$ ). 43.5% of patients had  $\geq 50\%$  improvement in the HAMD-17 at Week 8, with 39.1% of patients reaching remission (HAMD-17  $\leq 7$ ). Safety results were consistent with prior studies, with 8 patients reporting adverse events the most common being UTI and nausea.

**Conclusions:** Pimavanserin is associated with early sustained improvement of depressive symptoms in patients with PD and is well tolerated. These results are consistent with recently reported data of PIM in major depressive disorder. Additional placebo-controlled data is needed to further determine effectiveness.

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## Effectiveness on the balance and the walking of a program of home-rehabilitation by digital support versus paper on Parkinson's patients: A randomized controlled trial

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**Introduction:** Studies have shown the value of commercial games (Nintendo Wii, Kinect) as home-rehabilitation tools for improving the balance and quality of life of Parkinson's patients (PD). However, games specifically designed for rehabilitation needs and the capabilities of people with PD are needed for optimal effectiveness, adherence and security.

The objective is to evaluate the effects on the balance and the walk of a program of 3 months of home-rehabilitation guided by digital support (BYM system) or paper.

**Methods:** 31 patients with PD or related disease were included and randomized. The control group (n = 15) performed home-rehabilitation by exercises on paper booklet. The experimental group (n = 16) performed home-rehabilitation with the BYM system consisting of a tablet application coupled to a motion sensor. Both groups were instructed to perform 30 minutes of exercise per day for 3 months. Clinical performance was assessed before and 3 months after the beginning of the program.

**Results:** Both groups were comparable in pretest. At 3 months, the performance of walking tests was improved in the tablet group: + 14.7% on the 6min test (pre = 498.3m, post = 571.7m) + 18% on the comfortable 10m (pre = 9.1s, post = 7.4s) + 12.6% on the TimedUp& Go (pre = 9.5s, post = 8.3s) -34% on the UPDRS III (pre = 9.1, post = 6, 0). The performances of the booklet group are unchanged or even worse.

**Conclusions:** Although we have not been able to show a significant difference between the two groups, the results of this pilot study are encouraging. A larger study would be needed to confirm these results.

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## The PRO-GO study: A prospective, observational study to evaluate non-motor symptoms in Parkinson's disease patients treated with safinamide

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**Objectives:** Safinamide is an a-aminoamide with both dopaminergic and non-dopaminergic mechanisms of action. While the efficacy of safinamide in reducing OFF time and dyskinesia in patients with fluctuating Parkinson's disease (PD) has been established in several controlled studies, its effectiveness on non-motor symptoms and patient reported outcomes (PROs) when used in daily practice has been less well studied. The PRO-GO study is designed to evaluate the effectiveness of routine safinamide treatment for motor and non-motor symptoms, health status/QoL and treatment satisfaction in patients with PD.

**Methods:** This ongoing, observational study follows PD patients (30-80 years) with motor fluctuations routinely treated with safinamide for 2 months (with an optional 4-month extension). The decision to prescribe safinamide must have been made in accordance with the US package insert, and independently from, the decision to enroll the patient in this study. Patients can either be naïve to previous MAO-B inhibitor treatment or switched from adjunct therapy with a dopamine agonist or previous MAO-B inhibitor. Outcomes (at Day 60 and during follow-up) include motor, non-motor and QoL measures as assessed by the MDS-UPDRS (Parts I-IV), Clinical and Patient's Global Impression of Change Montreal Cognitive Assessment and the PDQ-39. Patients complete the Treatment Satisfaction Questionnaire for Medication at all post-baseline visits.

**Results:** As of February 2019, 36 of 250 planned patients have been enrolled at 24 movement disorders clinics across the USA. Overall, 75% of patients are male and the mean $\pm$ SD age is 67 $\pm$ 8 years. Mean $\pm$ SD time since diagnosis is 4.9 $\pm$ 3.3 years and mean levodopa dose is 628.5mg; n=30 are MAO-B inhibitor naïve and n=6 have switched from adjunct therapy with a MAO-B inhibitor.

**Conclusions:** This observational study will provide important prospective data for the effectiveness of routine safinamide treatment in the management of motor and non-motor symptoms.

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### Exploring emerging role of epigenetics landscape intercepting with Mediterranean diet and ketogenic diet and nutraceuticals at gut-microbiota-brain axis in enhancing outcome in Parkinson's disease

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**Introduction:** Recent evidence suggests that PD may start from the gut and ascend to the brain via alpha-synuclein spread. Dysbiosis of gut microbiota as influenced by diet intake can trigger inflammation underlying PD:gut-microbiota-brain axis. These findings call into question the emerging role of Epigenetics landscape: dietary intake and nutraceuticals in PD.

**The objective** of our study is fourfold:

1. to evaluate the evidence in support of epigenetics determinants in PD;
2. to review the specific pathways underlying the Mediterranean diet and ketogenic diets in selected PD studies;
3. to evaluate the feasibility of reclassifying diets and food groups within the epigenetic networks;
4. to examine whether nutraceuticals targeting histone modifications rescue motor symptoms of PD.

**Results:** In reviewing the literature, we identify the functional relevance of three components of epigenetics: DNA methylation, histone modifications and non-coding RNA in regulating the multiple genes related to PD: inflammation, apoptosis, neural repair, oxidative stress and autophagy, Epigenomics as-

sociation studies are complementary to genomic association studies to unravel interplay of genetics and environmental determinants. Preliminary clinical studies have shown that higher adherence to Mediterranean diet (MD) reduces PD risk. In contrast, non-adherence to MD triggers early onset. While the key ketone body: beta-hydroxybutyrate has been shown to behave as histone deacetylase inhibitor, ketogenic diet may encounter energy metabolic balance in PD.

In reviewing the epigenetics profiles of common diet groups in MD diet and in part ketogenic diet, we find the majority of food groups (fruits, vegetables, nuts, and fish and seafood groups) interact selectively with epigenetics network implicated in PD. Spices; black pepper, ginger, and garlic, curry, function as modulators of the three epigenetics network, Our group has shown that liposome-formulated curry and ginseng extract improve PD motor deficits via Sirtuin pathway.

**Conclusions:** Epigenetics-driven nutraceuticals and diet can improve motor and non-motor outcomes in PD.

### P 113

## Public health education

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Public health education and promotion also focuses on building evidence regarding how to teach and what to teach so as to effectively reach different populations with messages that are pertinent to public health. In order to build effective bodies of knowledge in public health, public health education and health promotion must be focused not only health promotion for individuals and populations, but education for the current and future workforces, as well. Professionals in public health education and health promotion are responsible for coordinating population-based health education and promotion interventions and programs using evidence-based approaches.

As such, these public health experts and specialists:

- Provide guidance and direct assistance through planning, implementation, and evaluation of population-based health education and promotion interventions
- Partner with community groups, organizations, and coalitions to support strategies that promote public Health

## Nonmotor symptoms, quality of life, and tolerability/safety with long-term levodopa-carbidopa intestinal gel treatment in advanced Parkinson's disease patients - interim data from the DUOGLOBE study

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**Objectives:** Evaluate safety and effectiveness of levodopa-carbidopa intestinal gel (LCIG) on nonmotor symptoms (NMS) and quality of life (QoL) in advanced Parkinson's disease (PD).

**Methods:** DUOGLOBE is the first multinational observational study of LCIG in routine care, including US, with 3-years follow-up. Assessments include NMS Scale (NMSS), Epworth Sleepiness Scale (ESS), PD Sleep Scale-2 (PDSS-2), PD Questionnaire (PDQ-8), and Modified Caregiver Strain Index. Serious adverse events (SAEs) were assessed. Visits occurred at baseline, and months (M) 3, 6, and 12 for this interim analysis.

**Results:** Sample sizes were limited over time, due to patients not yet achieving later visits. LCIG treatment improved NMS total score (NMS burden), daytime sleepiness, and sleep quality: mean decrease from baseline at 12-months: -26.4 NMSS, -2.3 ESS, and -2.7 PDSS-2, with greatest improvement in sleep/fatigue and mood/cognition NMSS subdomains. QoL significantly improved through month 12 (mean decrease: -8.8). Caregiver burden significantly improved through M6. Patients who did not complete 6M had slightly higher mean age, Hoehn & Yahr stage, and lower mean weight. At M12, 35% were on LCIG monotherapy. The safety dataset included 139 patients, 28% experienced SAEs, and 11% AEs that led to discontinuation. Higher age, but not gender and disease duration, led to more SAEs (31% vs. 17%).

**Conclusions:** In this interim analysis of the first multinational observational study with LCIG, improvements in QoL and NMS burden including mood and sleep were consistently observed through 12 months. Safety and tolerability in routine clinical practice was consistent with phase 3 studies, with low discontinuation rates, and no predictors for SAEs except advanced age. These findings indicate a positive long-term benefit-risk profile for LCIG treatment of NMS in advanced PD patients.

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## Olfactory hallucinations as a non-motor sign of Parkinson's disease - a cross sectional study

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**Objectives:** To describe the prevalence and characteristics of Olfactory Hallucinations (OlfH) in patients with Parkinson's Disease (PD) in a tertiary movement clinic

**Background:** Hallucinations are a non-motor feature of alpha synucleinopathies and occur in 20-50% of patients with PD. Due to a lack of awareness as well as paucity of structured questionnaires/tests that target psychosis assessment with an emphasis on olfactory hallucinations (OlfH), these are often missed during clinical consultations.

**Design and Methods:** Single site, cross-sectional, IRB approved study. Patients diagnosed with PD per UK brain bank criteria by a movement disorder specialist were consecutively enrolled with informed consent and completed a questionnaire and self-administered a University of Pennsylvania Smell Identification Test (UPSIT). Inability to understand the instructions due to language barrier or severe underlying pathology were exclusion criteria.

**Results:** 137 of the 147 (93%) patients surveyed completed both the UPSIT and the questionnaire. Of the 137, 37% were female. 25 (18.2%) patients endorsed OlfH, of which 16 (64%) were men. Hallucinations in other sensory modalities were also reported: Visual (16.7%), Auditory (9.48%) and Tactile (7.29%). In the patients with OlfH (n=25); concurrent sensory hallucinations included visual (32%), auditory (24%) and tactile (12%). 84% of patients with OlfH had a poor sense of smell objectively (UPSIT showed severe microsmia or anosmia) compared to 70% without OlfH, however this difference was statistically insignificant (p=0.199). The most commonly described hallucinations were "smoke/cigarette smoke". While most reported that OlfH were infrequent, 18% (n=2) reported hallucinations lasting >1 hour and found them unpleasant and upsetting.

**Conclusions:** Non-motor symptoms of PD are often missed in routine clinical practice and have far-reaching implications in patient care. OlfH tend to be under-reported with prevalence ranging from 2.1% to 10% in prior studies compared to 18.2% in our cohort. These patients also reported a higher frequency of concurrent sensory hallucinations.

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## Improving the quality of life of patients with Parkinson's disease using an eight week exercise program - a case control study

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**Background:** Parkinson's disease (PD) is the second most common, neurodegenerative disorder caused by a severe loss of the nigrostriatal dopaminergic neurons. Several interventions are used in order to lessen the morbidity associated with PD. Physical activity and exercise can complement pharmacological



therapy to manage the inherent decline associated with the disease. Recent research suggests that exercise programmes following diagnosis may alter neurophysiological processes, possibly slowing symptom progression,

**Aims:** Our study aims to assess the immediate and long term outcomes of an exercise program patients with Parkinson's disease

**Methods:** A case control study was conducted in Sir Ganga Ram Hospital, Lahore. 40 PD patients were included. Quality of life issues were evaluated by interactive qualitative interviews, Montgomery- Aasberg depression rating scale and Herth Hope Index before project start at 6, 12 and 18 months. Patients in exercise group undertook 8 week home based exercise program. The exercise program focused on improving strength and endurance of the back, abdominal muscles, lower extremities and mobility of the spine and hips.

**Results:** Functional tests showed stability in the exercise group compared to control group. Quality of life measures showed low values for depression compared to control group and emphasized the value of group training and the importance of collaboration with participants responses. Quality of life, general health status, lumbar mobility and behavioural status were greatly improved. Interview data suggest that a higher rate of follow-up on home training would further improve results.

**Conclusions:** We concluded that an eight week exercise program can improve quality of life, behavioural status and movement ability in patients with Parkinson's Disease. Our follow-up data from the 2 year period 2016-18 suggest benefit of group exercise program developed in collaboration with participants, effects becoming more marked over time. Further research to specify benefits of structured exercise is recommended.

**P 118**

## **Design, characterization and in vivo evaluation of intranasal delivery of levodopa loaded aerosol microsphere for Parkinsonism treatment**

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**Objectives:** Levodopa is the drug of choice in the treatment of Parkinson's disease but it exhibits low oral bioavailability and very low brain uptake. The present research work involves formulation development and evaluation of nasal mucoadhesive microsphere aerosol of levodopa in view to, improve bioavailability and reduce dosing regimen.

**Materials and methods:** The Microspheres were prepared by spray drying and cross-linking method using mucoadhesive polymers including chitosan salt, hydroxypropylmethylcellulose, hydroxypropylcellulose, sodium alginate and contained levodopa. Formulation parameters and processing parameters like ratio of drug to polymer and stirring speed were optimized. Microspheres were evaluated for particle size, drug content, swelling ability, percentage yield, In Vitro release characteristics and suitability for nasal drug delivery in terms of particle size and in vivo distribution after intranasal administration. The efficiency of levodopa microspheres aerosol to striatal transplantation and the altering of apomorphine-induced rotational behavior in the 6-hydroxydopamine unilaterally lesioned rat model were also tested.

**Results:** The average particle size of spray-dried and cross-linked formulations were found in the range between 10-30  $\mu\text{m}$  with percent mucoadhesion in the range of 90%-95%. In vitro drug release was found to be proportional to drug to polymer ratio. In vitro drug release for optimized formulation, that is, (F4), was found to be 94.56% at the end of 6 h. Release of drug from microspheres followed non-Fickian diffusion kinetics. Levodopa loaded microsphere aerosol groups exhibited lower rotation scores than microsphere groups as early as 1 week postlesion. These benefits continued throughout the entire experimental period and they were statistically significant during the 1, 2 and 8 weeks ( $p < 0.001$ ). The histopathological study indicates nonirritant nature of microsphere.

**Conclusions:** The results of this work indicate that intranasal aerosol microsphere of levodopa may be beneficial for the treatment of Parkinson's disease compared with other delivery routes reported earlier.

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## Correlation of insomnia to the quality of life of patients in Parkinson's disease

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**Objectives:** Evaluation of the incidence of insomnia, its association with motor, neuropsychiatric disorders

**Methods:** The study involved 100 patients (60 men and 40 women) diagnosed with PD without dementia, the average age was  $60.34 \pm 0.6$  years, the stage was  $2.24 \pm 0.5$ , and the PD duration was  $5.6 \pm 3.4$  years. Hoehn-Yahr stage evaluation, the unified PD assessment scale, Beck depression questionnaires, Spielberger anxiety, Parkinson's Disease Sleep Scale (PDSS), Euphoria sleepiness - Excessive Sleep Scale (ESS), Parkinson Fatigue Scale fatigue (PFS- 16), assessments of cognitive functions in PD (SCOB-Cog) - Scales for Outcomes of Parkinson's disease-Cognition (SCOPA-Cog), Lilly Apathy Rating Scale (LARS), a quality of life questionnaire under the PD - Parkinson's Disease Quality of Life were used

**Results:** Sleep disturbances were noted in 36% of patients, night awakenings with sleep fragmentation in 82%, early awakenings in 41% of patients. A greater frequency of disturbances of sleep, night awakenings, unpleasant dreams were noted in women. There was a tendency to intensify insomnia as the severity increased and the duration of PD increased. Patients with the onset of insomnia in the "premotor" stage of PD were statistically significant ( $p < 0.05$ ) differed from patients in other groups more low self-esteem of the quality of sleep, the severity of sleep disturbances, the greater frequency of nocturnal awakenings. Patients with sleep fragmentation statistically ( $p < 0.05$ ) were characterized by a greater severity of sleep disturbances and the frequency of early awakenings, lower sleep quality, ataxia, nocturia, morning drowsiness, the presence of unpredictable daily fluctuations.

**Conclusions:** Sleep disorders in patients with BP are heterogeneous - partly due to age factor, motor and non-motor disorders. Based on the multifactority of insomnia in PD, effective therapy of patients with sleep disorders should be individualized taking into account the nature of motor disorders, concomitant emotional disorders

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## **Safety of levodopa-carbidopa intestinal gel in advanced Parkinson's disease patients: Interim results of a US subset in the DUOGLOBE observational study**

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**Purpose:** Levodopa-carbidopa intestinal gel (LCIG) (also known in the US as carbidopa-levodopa enteral suspension [CLES]) is a long-term treatment option for advanced Parkinson's disease (PD), administered via percutaneous gastrojejunostomy (PEG-J) and an external pump. . In phase 3 studies, all tubes were placed by a gastroenterologist (GI). The objective of this interim analysis was to investigate routine clinical practice of PEG-J insertion, component replacements of the device, and associated safety.

**Methods:** DUOGLOBE is an ongoing, 3-year, observational multi-country study. This interim analysis included patients recruited at 19 US sites who had the PEG-J insertion procedure. The type of proceduralist performing the PEG-J, type of tubing used, frequency of tube replacements, and Serious Adverse Events (SAEs) were assessed. This analysis was not powered for between groups comparisons.

**Results:** Twenty-seven US patients were included. 16 (59%) had PEG-J insertion performed by a GI with 13 (81%) completing the first 6 months. 11 subjects (41%) had an interventional radiologist (IR) perform the procedure with 8 (73%) completing the first 6 months. There were no tube replacements required in 81.5% of patients during the first 6 months. Similar percentages of subjects had 0/1/2/3 tube replacements between the proceduralists (GI: 0-75%, 1-25%, 2-0%, 3-0%; IR: 0-90.9%, 1-0%, 2-9.1%, 3-0%) . Of 5 tube replacements, 4 were performed by a GI using AbbVie proprietary tubing and 1 was performed by an IR using non-AbbVie tubing. Most commonly reported treatment-emergent SAEs were abdominal pain 2 (7.4%) and dyskinesia 2 (7.4%).

**Conclusions:** This interim analysis of US patients in a multi-country observational study with CLES, limited by small patient numbers, GIs more frequently performed PEG-J insertion than IRs with similar percentage of subjects completing the first 6 months of the study. Frequency of tube replacements and AEs leading to drug withdrawn were similar between GIs and IRs.

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## Heterozygous mutation in parkin has no major impact on clinical follow-up in Perry syndrome

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**Objectives:** The Perry syndrome (PS) is a rare, neurodegenerative disorder with autosomal dominant inheritance caused by point mutations in *DCTN1* gene. It is characterized by parkinsonism, hypoventilation, weight loss and psychiatric symptoms. In this study we provide novel data about Polish family with *DCTN1* p.Gly71Glu mutation in heterozygous state

**Methodology:** Detailed clinical and neuropsychological data were obtained from this family. The neurological and neuropsychological examination were performed 6 times during 11 years of observation. Point mutations and the gene rearrangements were additionally analyzed in *PARK2*, *PINK1*, *DJ1*, *SNCA* and *LRRK2* gene.

Functional analysis of the *PARK2* p.Ala82Glu variant was performed in an established HeLa cell model before and upon treatment with the mitochondrial uncoupler CCCP by western blotting and high content imaging.

**Results:** The neurological examination demonstrated all cardinal features of PS with severe parkinsonism, levodopa induced motor fluctuations and dyskinesias, respiratory insufficiency with the exception of weight loss. Neuropsychological assessment revealed deterioration of working memory and learning. The patient demonstrated compulsive behaviours like shopping and eating (scored 21 on Frontal Behavioral Inventory: deficit behaviours 10, disinhibition 11), but only in "on" phase. The genetic studies showed the *PARK2* p.Ala82Glu and *DCTN1* p.Gly71Glu mutations, both in heterozygous state

The *PARK2* p.Ala82Glu variant showed no major defects in mitochondrial stress-induced activation or enzymatic activity as assessed by Parkin translocation, ubiquitin charging of the catalytic residue, or formation of phosphorylated poly-ubiquitin chains.

**Conclusions:** In this PS family the proband's neurological profile is compatible with PS syndrome, while behavioural and neuropsychological profile also include features of behavioural variant of FTD and impulse control disorder typical for Parkinson's disease. Functional analyses of the early steps of the *PINK1*-Parkin mitophagy pathway did not reveal any dramatic defects caused by the *PARK2* p.Ala82Glu mutation.

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## GBA-related PD can manifest with ichthyosis. A case report

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**Objectives:** To report the relationship of ichthyosis with GBA-related PD

**Methods and results:** A 34-year-old Filipino man was referred to our centre for dystonia-parkinsonism. He reported a 2-year history of low-frequency tremor in his left hand, along with rigidity, slowness and involuntary posturing of the left limbs, responsive to levodopa. He denied hyposmia, constipation and neuropsychiatric or sleep disorders. His neurodevelopmental milestones had been unremarkable. As only medical history, he reported a generalized cutaneous rash from the birth.

In the first evaluation, we observed mild parkinsonism on his left side, with some dystonic posturing of his left hand and right foot. The rest of the neurological exam was unremarkable. He had a macular brown-pigmented lesion on his limbs and torso, with a "cracked" appearance, suggestive for ichthyosis.

His 4-year younger sister had similar cutaneous lesions. The family history was otherwise negative for PD, dystonia or other neurologically-relevant conditions.

He was diagnosed with early-onset PD, and continued to be responsive to levodopa over the following years, with early development of dyskinesias and fluctuations. His brain MRI and neurophthalmologic evaluation were unremarkable, and the ichthyosis was confirmed by a dermatologist.

Genetic tests were negative for the common causes of early-onset autosomal-recessive PD. He was found positive for a heterozygous mutation in the GBA gene (c.437C>T (p.Ser146Leu)), previously reported in Gaucher's disease (GD), but never associated with PD.

**Conclusions:** Ichthyosis has been described in GD, but the relationship with the status of GBA heterozygous mutation carrier has not been reported. This finding further expand the clinical manifestations of this condition, and we believe that this cutaneous hallmark, could provide a hint for suspecting GBA mutations in PD subjects. More studies are needed to confirm this relationship.

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## Hung-up knee jerk reflex" description in a population of Mexican patients with Huntington's disease

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Describe the HUKJR in patients genetically diagnosed with HD from the Instituto Nacional de Neurología y Neurocirugía (INNN) of Mexico City, as well as its clinical correlation with the Unified Huntington Disease Classification Scale (UHDRS). Hung-Up Knee Jerk Reflex (HUKJR) is a clinical sign in the physical examination of Huntington's Disease (HD)[1]. The reflex is associated with the involuntary contraction of the femo-

ral quadriceps, caused by the percussion of the patellar tendon; in the HUKJR the extension of the leg remains elevated for a prolonged moment and relaxes sharply until reaching its original place. This sign is due to a choreic movement caused by delayed sensitivity[2]. The literature describes a prevalence of 80% in HD vs controls[3]. There are no studies in Latin America.

It is important to consider HUKJR in the physical examination of HD. It could be a pathognomonic sign, it can occur in presymptomatic stages, it has been observed in advanced course of the disease, a decrease in the reflex probably by the progression towards Parkinsonism. It is necessary to conduct studies in a larger population and with choreas of other etiologies to confirm or discard the before mentioned.

#### P 130

### Survey of the use of cannabis and its derivatives by patients with Parkinson's disease and its association with psychosis

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**Objectives:** Interest in cannabis for both medical and recreation use has increased recently; within the past decade medical use of cannabis has been legalized in 33 states. Cannabis has been used as treatment in a federally unregulated fashion for chronic pain, insomnia, epilepsy, tremor, Parkinson's disease (PD) among other conditions. We hypothesize hallucinations would be greater in PD using cannabis as up to 50 % of PD patients develop hallucinations at baseline. We conducted a survey for use of Cannabis or other CBD/THC containing equivalent in a cohort of PD patients.

**Methods:** A 15 question was distributed to PD patients who presented for routine follow-up. This questionnaire requested basic demographic information without identifiers, history of use of cannabis or its derivatives, frequency of use, reason for use, information regarding history of PD and if the patient has a history of psychosis or other psychiatric conditions.

**Results:** A total of 21 patients completed the survey. Of those who completed the survey, 5 (24%) endorsed a history of use of cannabis or its derivatives. There were 3 patients (14%) who actively used cannabis or its derivatives. Ten (50%) patients endorsed a history of hallucinations. Two out of the three who were active users of cannabis or its derivatives reported hallucinations.

**Conclusions:** From these data, we do not have enough information to determine if there is an association between use of cannabis and psychosis in PD. An association is suggested although the sample size is small. Given the recently increased interest in the use of cannabis by patients to self-treat symptoms of PD, further research into the association of the use of cannabis with likelihood of psychotic experiences is warranted to ensure safety for the more vulnerable PD population.

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## Neuroprotective effect of Pinitol on rotenone and 6-OHDA induced Parkinson's disease

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**Background:** The present study was intended to investigate the protective effect of Pinitol against Parkinson's disease through the use of rotenone-induced neurotoxicity model.

**Methods:** The effect of Pinitol was examined via behavioral function, Tail suspension test, morris water maize test and cylinder tests. Pinitol effect was also studied on the several biochemical and histological markers related to Parkinson's disease in animal and cell culture models. Histopathological examination of the test animal brain was carried out by using Haematoxylin and Eosin staining. Pinitol effect was also using cell culture model with use of brain endothelial cells. The flow-cytometric analysis was carried out to measure effect of Pinitol on apoptosis in cell culture model.

**Results:** The abnormal level of antioxidant enzymes and lipid peroxidation were restored to normal after Pinitol treatment. Furthermore, intracellular ROS level and apoptosis were found to be reduced following Pinitol treatment. During the 6-OHDA induced PD, the level of antioxidant marker such as GSH, ROS and TBARS, found to be significantly modulated by the Pinitol.

**Conclusions:** It may be suggested that Pinitol may be used as therapeutic agent against Parkinson's disease.

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## Risk of ICD in Parkinson's disease patients - a retrospective study

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**Objectives:** To describe the prevalence of Impulse Control Disorders (ICDs) in South Indian PD population. To establish association between these disorders and the LEDD along with other related factors as a part of clinical progression of disease.

**Background:** ICDs are common in PD and associated with loss of independent decision making. Understanding the relation between the progression of disease, medical management of symptoms and ICDs will assist in effective early management of the same.

**Rationale:** In Parkinson's disease (PD), ICDs are closely related to use of dopaminergic medications, and most commonly include pathological gambling, excessive spending, hypersexuality and over-eating. The prevalence of ICDs in PD is not precisely known. ICDs in PD appear in large part to be induced by dopaminergic medications, via disturbance of the reward system. Medical literature supports a strong association between impulse control disorders and anti-parkinsonian medication, especially the dopamine agonists.

**Methodology:** A total of 120 PD patients on anti-Parkinson's medication attending Department of Neurology, NIMS, Hyderabad, participated in the study. UPDRS, Stroop test, PDQ 39, MoCA and QUIP-RS were administered to the patients after collection the medical history.

**Results:** Results from the current study indicate that there is a significant relationship between the Total ICD, QUIP-RS scores and LEDD in the study population. Relationship varied, but was still positive between QUIP-RS score and LEDD for Dopamine agonists and other Parkinson's Medication when dopamine agonists were excluded. Relationship was negative for Total ICD score when Dopamine Agonist were not considered in LEDD. 52.5% of the study populations had dyskinesia and 25% had Dystonia.

**Conclusions:** Variables associated with ICDs include, male sex, younger age and personal or family history of alcoholism or gambling apart from medication. Symptoms of irritability and depression were also associated with the presence of these behaviors.

### P 135

## Cognitive functions study in patients with Parkinsonism in Uzbekistan

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**Objectives:** To give a comparative description of neuropsychological features in primary and secondary parkinsonism.

**Material and methods:** We examined 29 patients, 15 of them were diagnosed with primary parkinsonism, 14 of them had secondary parkinsonism. For the study of cognitive functions in patients with Parkinsonism, the MMSe scale was used, affective disorders were the hospital scale of anxiety and depression of HADS, the nonspecific SF-36 questionnaire.

**Results:** When assessing the level of cognitive functions, it was revealed that the total indices of the physical and psychological components of health were significantly ( $p < 0.05$ ) higher in the comparison group ( $48.1 \pm 3.23$  and  $51.1 \pm 2.98$  points, respectively) than in basic ( $31.2 \pm 0.53$  and  $32.8 \pm 0.8$  points, respectively), and the difference between them was minimal in both groups. Meanwhile, the index of role functioning due to the psychological component (Re) in men was significantly higher ( $p < 0.05$ ), and the indicator of pain intensity (BP) in women was significantly lower ( $p < 0.05$ ). The level of anxiety-depressive disorders in patients with primary parkinsonism was significantly ( $p < 0.05$ ) higher than in patients with secondary and comparison groups. Tender analysis of anxiety and depression showed their statistically significant ( $p < 0.05$ ) increase in women compared with men.

**Conclusions:** Neuropsychological characteristics of patients with Parkinsonism depends on the etiologic factor. The degree of cognitive deficits in secondary parkinsonism is more pronounced than in the primary parkinsonism and does not have sex differences.



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## The possible neuroprotective propensity of protocatechuic acid and *Prosopis cineraria* combinational approach against rotenone induced Parkinsonism in rodents

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**Objectives:** The current study was envisaged to investigate the synergistic therapeutic effect of naturally occurring bioactive phenolic acid, i. e., protocatechuic acid and hydroethanolic extract of *Prosopis cineraria* combination (PA+ HEPC) in rotenone induced behavioral, neurotransmitter, oxidative as well as mitochondrial deficit mouse model of Parkinsonism.

**Methods:** Mice were randomly divided into five groups. (PA+ HEPC) combination (100, 200 and 400 mg/kg, p.o.) accompanied with rotenone (1 mg/kg i.p.) injection, saline and rotenone (1 mg/kg i.p.) alone were administered in respective group for 21 days. Rotenone treated group exhibited significant impairment in memory and learning behavior, locomotor activity. Additionally, reduction in enzymatic antioxidant level such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxide (GPx), acetylcholinesterase (AChE) and dopamine levels as well as mitochondrial dysfunction via decrease in Complex-II and Complex-III (Succinate Dehydrogenase, MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-Htetrazolium bromide, respectively) enzyme activity was observed in mice brain as compared to control group.

**Results:** Behavioral test as well as biochemical estimation demonstrated that pretreatment with (PA+ HEPC) combination significantly reversed ( $p < 0.01$ ) rotenone induced damaging effect as compared to rotenone group in a dose dependant manner.

**Conclusions:** Neuroprotective effect of (PA+ HEPC) combination may be utilized as a beneficial therapeutic tool for the Parkinson's disease management.

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## Effects of recreational therapy and speech therapy among participants with Parkinson's disease and Parkinson plus conditions: Findings from a 16-week multidisciplinary program

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**Objectives:** Parkinson's disease (PD) is a multimodality disorder associated with changes in gait, speech, cognition, psychological well-being and overall quality of life. People with PD have two times higher risk of falling when compared to individuals with other neurological disorders (Allen et al., 2013). In addition, 70-80% of individuals with PD experience speech changes that is noticeable to others (Miller et al., 2012). Therefore, the aim of our study is to examine effects of a multidisciplinary intervention including recreational therapy (RT) and speech therapy among individuals with PD or PD plus conditions during a 16-week community program.

**Methods:** Current participants include 4 men and 2 women with idiopathic PD, including two with deep brain stimulation. The mean disease duration for participants is 5.5 years and all participants are either in mild or moderate stages of PD (Hoehn & Yahr Scale scores:  $M = 2016$ ,  $sd = 0.82$ ). All participants attend a weekly LOUD Crowd<sup>®</sup> program consisting of different speech and cognitive activities with a goal of improving functional communicative ability (Boutsen et al., 2018). In addition, the RT intervention focuses on fall prevention education and implementing a balance, strength, and endurance routine targeting musculoskeletal, somatosensory, vestibular, and visual components.

**Results:** Descriptive statistics were calculated to establish participants' baseline performances. Assessments included Dementia Rating Scale ( $M = 135.83$ ;  $sd = 3.76$ ), Voice Handicap Index ( $M = 47.5$ ;  $sd = 20.68$ ), Timed-up-and-Go ( $M = 11.42$ ,  $sd = 2.06$ ), Biodex Balance System ( $M = 1.43$ ,  $sd = .41$ ), Modified Falls Efficacy Scale ( $M = 8.46$ ,  $sd = .48$ ), and the Hospital Anxiety and Depression Scale (Anxiety=  $M = 5.67$ ,  $sd = 3.01$ ; Depression  $M = 7.00$ ,  $sd = 2.19$ ).

**Conclusions:** A multidisciplinary intervention program is expected to improve fall risk, maintain speech and cognitive functioning and improve quality of life among PD participants.

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### Quality of life of the patient with parkinson's disease before and after the implementation of the deep cerebral stimulator (DBS)

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Parkinson's disease (PD) is a chronic and neurodegenerative disease, caused by a degeneration of dopaminergic transmission, manifested by: bradykinesia, tremor at rest, and stiffness. The deep brain stimulator (DBS) is used when the EP meets the surgical criteria for placement. One of the therapeutic goals is the improvement of the quality of life (QoL), and this can be easily measured with the PDQ-8 scale, where among the most points the QoL has the most deficient. Likewise, it seeks to reduce the dosage of levodopa to cause less adverse effects to the patient.

We included 10 patients (4 women) with a mean age of onset of PD of  $42.1 \pm 12.3$  years, and a mean evolution time of  $11.4 \pm 5.44$  years until the time of surgery. The PDQ-8 score prior to surgery was  $34.37 \pm 23.57$  points, and the levodopa dose of  $1075.9 \pm 295.11$  mg. At one year of follow-up, the mean PDQ-8 score was  $20.66 \pm 18.32$ ; and the equivalent dose of levodopa  $257 \pm 133.5$  mg. The parametric tests were not significant for the results of the PDQ-8 test (IC = 95%,  $p = 0.83$ ), however, in the dosage of levodopa if significance was found (CI = 95%,  $p = 0.007$ ).

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## Parkinson's disease and Abelson tyrosine kinase inhibitor, Nilotinib: Two case reports in Vietnam

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**Objectives:** We evaluated the safety and efficacy of Nilotinib, an Abelson (Abl) tyrosine kinase inhibitor, in two patients with Parkinson's disease (PD).

**Methods:** Two patients fulfilled the 2015 MDS clinical diagnostic criteria for "clinically established PD" and received oral Nilotinib 200 mg daily for 24 weeks. Disease progression was monitored every 4 weeks by measuring the patient's motor and non-motor symptoms with the Unified Parkinson's Disease Rating Scale (UPDRS). Mini Mental State Examination (MMSE) was used to screen for cognitive impairment.

**Results:** The patients experienced some non-serious adverse events (AEs), including nausea and mild headache. However, these AEs resolved with continued administration of the drug. There were no serious AEs during the drug administration. By the end of 24 weeks, an average decline of 6.5 points and 3 points in the UPDRS and UPDRS-III, respectively, was observed compared to baseline.

Furthermore, the patients showed improvement of non-motor symptoms, such as swallowing and constipation. MMSE results were normal throughout treatment.

**Conclusions:** Our results suggest that Nilotinib 200 mg once daily may be safe and effective for PD patients.

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## Neuroprotective effects of rolipram against experimental Parkinsonism in mice

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**Objectives:** Parkinson's disease (PD) is a neurodegenerative disease and a movement disorder characterized by loss of dopaminergic neurons in the substantia nigra causing dopamine depletion in the striatum. Rolipram, a specific inhibitor of the phosphodiesterase IV (PDE IV), has recently been shown to exert neuroprotective effects in an Alzheimer transgenic mouse model and in hypoxic-ischemic damage in the rat brain.

In the present study, we tested neuroprotective effects, if any, of rolipram drug, a specific inhibitor of the phosphodiesterase IV in 1-methyl- 4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in mice.

**Methods:** Experimental animal is muscular weighing 25-30 g of 4-5-month-old. The drug was given four times at 12 h intervals by gavage (25-100 mg/kg) in animals made parkinsonian following two doses of MPTP (30 mg/kg, i.p.). Control mice were injected with the same volume of pure DMSO. MPTP-induced striatal dopamine depletion was significantly attenuated by higher dose of rolipram. MPTP-induced catalepsy and akinesia, as well as loss in swim ability, were blocked dose-dependently by rolipram. Brain was used for biochemical and histopathological study.

**Results:** Present study further shows that rolipram can dose-dependently attenuate both in vitro hydroxyl radical production in a Fenton-like reaction, and also ex vivo 1-methyl-4-phenylpyridinium (MPP<sup>+</sup>)-induced hydroxyl radical generation in isolated mitochondria. These results indicate that the observed neuroprotective effects of rolipram stem from its significant antioxidant action.

**Conclusions:** The preliminary results suggest that rolipram is a neuroprotector, and mechanism other than lipid lowering action could be the basis of this effect. Present data show a neuroprotective effect of the PDE IV specific inhibitor rolipram against dopaminergic neuron degeneration, suggesting that PDE IV inhibitors might be a potential treatment for Parkinson's disease.

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## Clinical-instrumental algorithm for assessment visuospatial dysfunction in patients with Parkinson's disease

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**Aims:** To study the features of visual spatial dysfunction (VSD) in patients with Parkinson's disease (PD) using modern clinical-neuropsychological, ophthalmological and neuroimaging methods.

**Methods:** Two groups: 1st(79 pers., ages 65,8±8,5)-patients with PD, 2nd (34 pers., ages 64,2±4,7)-patients without PD (control group) were examined. Neurological and ophthalmological examination, neuropsychological examination: Yerkes test, mirror test "mirror numbers and letters" and "clock hands" by Luria, "noisy" images (R. Sells), reduced test of Raven's progressive matrices, Poppelreuter test; cognitive functions (MMSE, FAB (Frontal assessment battery, CDR (Clinical Dementia Rating); optical coherence tomography (OCT, protocols-Ganglion Cell Complex (GCC), Retinal Nerve Fiber Layer (RNFL), Macular Map 5 (MM5)); MRI morphometry were performed.

**Results:** The thinning of the retinal sections of the eye assessed by OCT (thickness of the lower part of the retinal ganglion cell complex (89,1±7,2µm versus 96,1±7,6µm,  $p < 0,01$ ), lower quadrant of the layer of nerve fibers of the retina (121,3±17,5 µm versus 124,9±15,6 µm,  $p < 0,05$ ), the central fossa (278,5±17,2µm versus 286,8±18,8µm,  $p < 0,05$ ) and the upper hemisphere of the paracentral zone (319,9±14,4 µm versus 328,6±15,1 µm,  $p < 0,01$ )) and the cerebral cortex atrophy assessed by MRI morphometry (calcarine sulcus ( $p < 0,01$ ), parietal-occipital sulcus, inferior occipital gyrus and sulcus ( $p < 0,05$ )) were the most significant for the development of VSD in PD. The risk of VSD (visual agnosia, illusory optic-spatial phenomena, hallucinatory optic-spatial phenomena) increased with the development of dementia ( $p < 0,05$ ).

**Conclusions:** VSD in PD can be caused by changes in the light-transmitting systems of the eye, morphological changes in certain layers of the retina and degeneration of the neurons of the parietal and occipital cortex of the brain. Diagnostics of VSD in PD should be carried out clinical-neuropsychological tests (Poppelreuter test, reduced test of Raven's progressive matrices, Yerkes test, MMSE, FAB), OCT (GCC, RNFL, MM5) and, in some cases, Brain MRI.

## Intensity-based exercise groupings in Parkinson's disease: Analysis from the Parkinson's foundation quality improvement initiative (PF-QII)

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**Objectives:** To describe duration and intensity-based exercise groups in individuals with Parkinson's Disease (PD).

**Background:** Evidence suggests that regular exercise slows functional decline in individuals with PD. There are limited data characterizing the impact of exercise intensity. The PF-QII dataset's recent inclusion of exercise duration and intensity data enables further exploration.

**Design and Methods:** All individuals with PD enrolled in the PF-QII registry with at least one New Data Collection Form were used to identify participants' exercise characteristics. Participants were first grouped by exercise duration (0hrs/wk, < 2.5hrs/wk,  $\geq 2.5$ hrs/wk). A second grouping used K-means clustering with individuals' self-reported exercise intensity. Analysis of variance and Chi-squared tests were used to compare participants' characteristics across groups.

**Results:** A total of 5,203 participants were included in analysis. The K-means cluster analysis identified four distinct intensity-based groups: Almost-none, Light-dominant, Moderate-dominant, and Vigorous-dominant. Light-dominant participants had greater exercise duration ( $24 \pm 10$  hrs/wk) compared to Moderate- and Vigorous-dominant (both  $8 \pm 4$  hrs/wk). Participants in both Vigorous-dominant and Duration Category  $\geq 2.5$ hrs/wk were more likely to be male, younger, better educated, and newly diagnosed, with fewer comorbidities, and better disease status ( $p < 0.0001$ ). After controlling for age, Hoehn & Yahr stage, years since diagnosis, and cognitive status, both duration and intensity groupings showed a significant correlation of improved scores on The Modified Caregiver Strain Index (MCSI) and Parkinson's Disease Questionnaire (PDQ-39) in high exercise groups compared to low exercise groups ( $p < 0.05$ ). No significant correlation was found between exercise grouping and hospitalization/ER visits, fall frequency, motor fluctuations, or dyskinesias.

**Conclusions:** Grouping exercisers with PD by intensity in addition to duration of exercise provides valuable insight into the differences between exercise categories. Next steps include longitudinal analyses of change in outcomes related to exercise intensity group.

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## Evaluations of additive effect of two indigenous medicinal plants *Cedrus deodara* and *Mucuna pruriens* towards the treatment of Parkinson's disease

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**Objectives:** Parkinson's disease is the second most common neurodegenerative disease ranking next to Alzheimer's disease. Recently, the focus of PD's treatment has shifted towards herbal medicines. In this Study we evaluated additive effect of combined powder extract of *Mucuna pruriens* and *Cedrus deodara*. *Mucuna Pruriens* (Mp) is traditional herbal medicines known to have neuro-protective effects due to the L-DOPA while *Cedrus deodara* is used traditionally as a neuro-protective drug.

**Methods:** Parkinson's disease was induced by administering haloperidol (2.0 mg/kg i.p.) Daily for a week. The mice were divided into 5 groups (n=6). Group I received haloperidol (2mg/kg body weight). Group II received combination of levodopa and carbidopa (100mg+ 10mg/kg by i.p along with haloperidol) and Group III received combined powder extract of *Mucuna pruriens* (Seed) and *Cedrus deodara* (Stem bark) (MPCD) of (400mg/kg by p.o), Group IV received extract of *Mucuna pruriens* (Seed) alone at a dose of 500mg/kg (p.o.), respectively for 15 days along with haloperidol. Behavioural changes caused by haloperidol were studied by rotarod test, grip strength test and locomotor activity by actophotometer.

**Results:** The increased cataleptic scores (induced by haloperidol) were significantly ( $P < 0.001$ ) found to be more reduced with the combined powder extract of *Mucuna pruriens* (Seed) and *Cedrus deodara* (Stem bark) at a dose of 400mg/kg (p.o.) as compared to *Mucuna pruriens* (Seed) extract alone at a dose of 500mg/kg (p.o.).

**Conclusions:** From the findings of the performed models we can conclude that combined powder extract of *Mucuna pruriens* (Seed) and *Cedrus deodara* (Stem bark) shows better anti-parkinson activity as compared to *Mucuna pruriens* (Seed) extract and might be useful as a better and safer herbal alternate for management of Parkinsonism.

**Keywords:** *Mucuna pruriens*, *Cedrus deodara*, Parkinsonism, Additive

**Healthy control normalized acoustic speech and voice task performance in Parkinson's disease from the ontario neurodegenerative disease research initiative (ONDRI) study**

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**Objectives:** To investigate articulatory and phonatory measures of motor speech performance in a large cohort of individuals with Parkinson's disease (PD).

**Background:** Maximum effort (e.g., sustained vowel /ah/) and diadochokinetic tasks are common assessment measures in PD. From these tasks, a number of acoustic articulatory and phonatory measures can be extracted (Patel et al., 2018). Despite their importance diagnostically and as clinical outcome measures there are few large-scale studies that incorporate these measures. Thus, our understanding of typical PD performance on these tasks, relative to published healthy control normative values, is limited.

**Methods:** Data were collected from 140 participants with idiopathic PD (*M* age = 67.74 yrs.; *M* disease duration 8.39 yrs.; *M* Hoehn & Yahr = 2.09) participating in a longitudinal observational cohort study at multiple tertiary care centres. Using a head-worn microphone (cardioid pattern) positioned 2 cm from the mouth, data were recorded using an USB pre-amp connected to a laptop running an open-source audio software program. Analyses were conducted in Praat using standard procedures (Boersma, 2013; Boersma & Weenink, 2018; Maryn & Zarowski, 2015). Participants performed three trials each of a sustained vowel /ah/, alternating (/pa/, /ta/, /ka/), and sequential (/pa ta ka/) motion rate tasks. Task-averaged values for all measures were converted to standardized scores using robust age and sex-specific healthy control normative data from the extant literature.

**Results:** Values for all measures are reported as means, standard deviations, and z-scores calculated from extant normative data (Figure 1).

Variable	Mean Raw (SD)	z-score* (SD)
Maximum Phonation /ah/ (duration seconds)	16.50 (7.63)	-0.55 (1.12)
Maximum Phonation intensity (dB SPL)	70.31 (4.53)	-90 (1.03)
Maximum Phonation Mean F0 (Hz)	155.12 (49.16)	0.19 (1.04)
Maximum Phonation Mean jitter	0.01 (0.01)	N/A
Maximum Phonation Mean shimmer	0.04 (0.03)	N/A
Maximum Phonation harmonic-noise-ratio	21.62 (4.39)	-0.38 (0.01)
Sequential motion rates (/pa/ per second)	6.08 (1.13)	-1.02 (1.46)
Sequential motion rates (/ta/ per second)	6.02 (0.92)	-1.46 (2.05)
Sequential motion rates (/ka/ per second)	5.65 (0.84)	-0.75 (1.13)
Alternating motion rates (/pa ta ka/ per second)	5.95 (1.52)	-0.11 (1.07)

[Figure 1. Acoustic Speech/Voice Data]

**Conclusions:** Our results suggest that in early-mid stage PD, only articulation speed differed from healthy controls (z-score < -1.0) when data were controlled for age and sex differences. These data highlight the importance of using age and sex-adjusted data when evaluating speech/voice issues in PD.

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## Cognitive dysfunction in patients with Parkinson's disease and psychosis

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**Objectives:** Psychosis is one of the debilitating non-motor symptom of Parkinson's disease (PD) which commonly manifests through minor hallucinations (such as passage hallucinations, presence hallucinations, and illusions) and well-formed visual hallucinations. Cognitive impairment is strongly associated with psychosis in PD (PD-P). This study aims to explore the pattern of cognitive dysfunction in PD-P by comparing the cognitive characteristics of PD-P with those without psychosis (PD-NP) and healthy controls (HC).

**Methods:** This study recruited a total of 150 subjects (PD-P: 50, PD-NP: 50, HC: 50). Assessment of the global cognitive function was done by the Montreal cognitive assessment scale (MoCA). A set of neuropsychological tests assessed several cognitive domains that include executive functions [frontal assessment battery (FAB) and Stroop test], attention (Color trail and digit span), visuo-spatial functions [Rey's complex figure test (CFT), memory and learning [Rey's auditory and verbal learning test (RAVLT)], language (animal naming test) of all the subjects.

**Results:** The three groups were matched for age, gender, and years of education. HC had better performance in the tests assessing the global cognitive function (MMSE and MoCA) compared to both patient groups. However, both PD-P and PD-NP had similar MoCA scores. In all the tests, PD-P group had poor performance compared to PD-NP; however, the differences were significant in FAB, RAVLT trial-5, RAVLT-total learning, RAVLT (IR and DR), and CFT (copy, immediate and delayed recall).

**Conclusions:** Patient with PD-P have significantly poor cognitive function compared to PD-NP. The cognitive domains that were significantly affected in the PD-P were executive functions, memory and learning, and visuo-spatial functions. Although this study reinforces the association of PD-P with cognitive impairment, additional longitudinal studies are warranted to understand the natural course of these two NMS and relationship.



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## Impact of khat use among Parkinson's disease patient in Black Lion Hospital

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**Background and Information:** Khat, a plant that contains amphetamine like stimulants called cathine and cathinone, is widely distributed and abused in east Africa and mainly in Ethiopia. It is a herb taken for its recreational value to increase alertness and boost Energy with less addictive influences. So far there is no data that shows any benefit or risk to patients with Parkinson's disease

**Objectives:** Evaluate cathine and cathinone's effect on alertness, energy, sleep pattern, and tremor among Parkinson's disease patient

**Methods:** We recruited 120 age, sex, literacy level and functional status matched Parkinson's disease patients from Black lion Hospital from January, 2018 to September, 2018 and identified 2 groups such as Khat users and non-user. We then developed a questionnaire that address their symptoms and interviewed them to describe their experience with the herb on their alertness, energy, sleep pattern and tremor.

**Results:** Baseline characteristics like age, sex, literacy level and functional status were all comparable. Khat users were 53(44.16%) and non khat users were 67(55.8%). There was a satisfactory increased alertness and energy for activities among khat users (OD of 2.31, 95% CI 1.61-2.45) and a significant increment in tremor and sleep disturbance (OD of 1.24, 95% CI 0.93-1.45) compared to non khat users.

**Conclusions:** Amphetamine like substances like Cathine and cathinone in Khat improve Parkinson's disease patient's alertness and energy for activities while worsening tremor and sleep disturbances.

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## MiR-153 and miR-223 in Parkinson's disease: From brain to periphery

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Dysregulated microRNAs (miRNA) play a major role in developmental brain disorders, normal aging and various neurodegenerative conditions, including Parkinson's disease (PD). These short noncoding RNA species bind to the 3' untranslated region (3'-UTR) of target genes, resulting in targeted mRNA cleavage and protein translation repression.

A recent study employing miRNA microchip assays on *HMOX1*- and sham-transfected primary rat astroglia showed that altered expression profiles of salient miRNAs and their mRNA targets contribute to neural damage accruing from the overexpression of glial heme oxygenase-1 (HO-1). HO-1, a stress protein that catalyzes the conversion of heme to biliverdin, carbon monoxide and free ferrous iron, has been implicated in PD pathogenesis.

The advent of parkinsonian transgenic GFAP.HMOX1 mice, engineered to overexpress the human HO-1 gene (*HMOX1*) in astrocytes between 8.5 and 19 months of age, has facilitated our investigation of key miRNAs implicated in PD. The latter include miRNAs impacting neurodegenerative processes (oxidative stress, apoptosis, autophagy) and, more specifically, the hallmarks of PD (dopaminergic neuron degeneration, alpha-synuclein aggregation). Downstream of HO-1 overexpression, miR-153 and miR-223 were found to directly regulate alpha-synuclein. MiR-153 and miR-223 were significantly downregulated in GFAP.HMOX1 basal ganglia, correlating with increased alpha-synuclein mRNA and protein. Additionally, serum concentrations of both miRNAs progressively declined in the wild-type (WT) and GFAP.HMOX1 mice between 11 and 19 months of age. At each time point surveyed, circulating levels of miR-153 were significantly lower in TG animals compared to WT controls.

Moreover, in a diagnostic trial, miR-153 and miR-223 were similarly decreased in the saliva of human PD subjects compared to healthy controls.

These findings underscore HO-1-mediated perturbations in brain and peripheral miRNA expression profiles as a driver of PD neuropathology and implicate glial HO-1, miR-153 and miR-223 as potential diagnostic markers and targets for disease-modifying therapy in this condition.

# Topic: Other Parkinsonian Disorders

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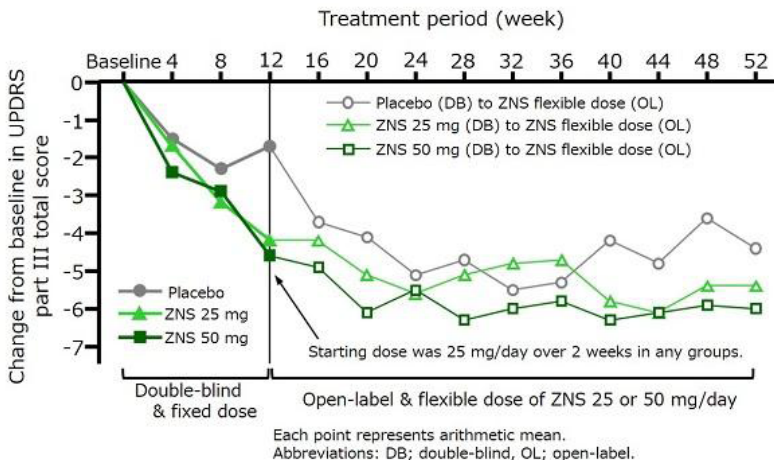
## Zonisamide improves parkinsonism in dementia with Lewy bodies: An open-label extension of a phase 3 randomized, controlled trial

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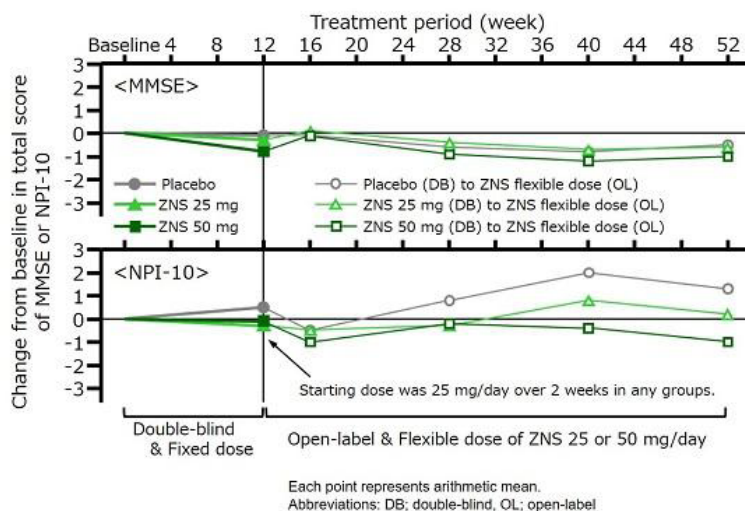
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**Objectives:** To evaluate the long-term efficacy for parkinsonism and tolerability of zonisamide (ZNS) in patients with dementia with Lewy bodies (DLB)

**Methods:** Outpatients diagnosed with probable DLB were randomized into 3 groups (placebo, ZNS 25 and 50 mg/day) and then treated with fixed dose of test drugs for 12 weeks in a double-blind (DB) manner. Subsequently, all patients received 25-mg/day ZNS over 2 weeks and then the flexible dose (25 or 50 mg/day) was allowed according to patients' conditions in a 40-week, open-label (OL) extension phase. The efficacy (UPDRS part III, MMSE and NPI-10) and safety were evaluated.



[Figure 1: Change from baseline in UPDRS part III total score]



[Figure 2: Changes from baseline in MMSE and NPI-10 total scores]

**Results:** After randomization, 346 patients who took ZNS at least once after the DB phase were included in the analyses (At baseline; mean age, 77.2 years; mean durations of dementia and movement dysfunction, 3.6 and 2.7 years; mean levodopa dose, 251 mg/day). Approximately 60% of patients took ZNS 50 mg more frequently than 25 mg in the final 4-week period. The score reduction in UPDRS part III continued until 24-28 weeks around, and then the score maintained until the final evaluation time point (figure 1). No remarkable score change in MMSE or NPI-10 showed throughout the trial (figure 2). Adverse events newly developed in the OL phase or largely increased compared with those developed in the DB phase were not found.

**Conclusions:** ZNS shows the long-term efficacy for DLB parkinsonism without deterioration of cognitive function, BPSD and safety in DLB patients.

P 153

# Efficacy and safety of zonisamide in patients with dementia with Lewy bodies with parkinsonism: Pooled analysis of phase 2 and 3 trials

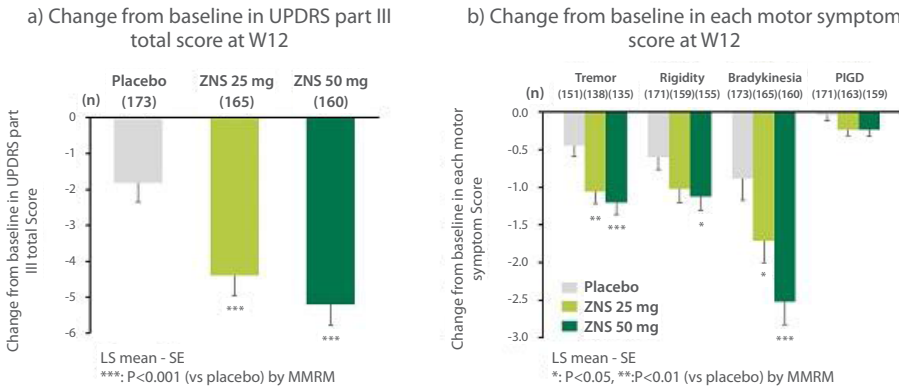
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**Objectives:** To characterize the efficacy and safety of zonisamide (ZNS) in patients with dementia with Lewy bodies (DLB) with parkinsonism, a pooled analysis of two trials (multicenter, randomized, double-blind, parallel-group, placebo-controlled trials) was performed.

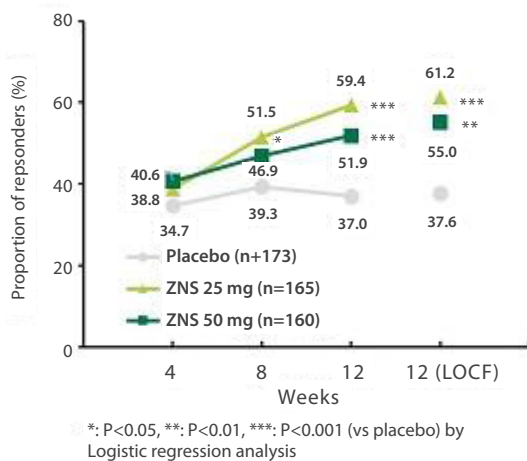
**Methods:** In efficacy analysis (n=498), ZNS (25 or 50 mg) was compared with placebo in terms of (1) changes from baseline in UPDRS part III total and subscale (i.e., tremor [UPDRS items 20, 21], rigidity [UPDRS item 22], bradykinesia [UPDRS items 23, 24, 25, 26, 31], and postural instability/gait disturbance [PIGD, UPDRS items 29, 30]) scores at week (W) 12; (2) the responder (defined as  $\geq 10\%$  improvement in UPDRS part III total score) proportion at W4, W8, W12 and W12 (last observation carried forward [LOCF]); and (3) changes from baseline in MMSE and NPI-10 total scores at W12. In safety analysis (n=508), ZNS was compared with placebo in terms of the incidence proportions of adverse events.

**Results:** ZNS significantly reduced UPDRS part III total, tremor, rigidity (on ZNS 50 mg only), and bradykinesia scores (figure 1).



[Figure 1: Efficacy for parkinsonism]

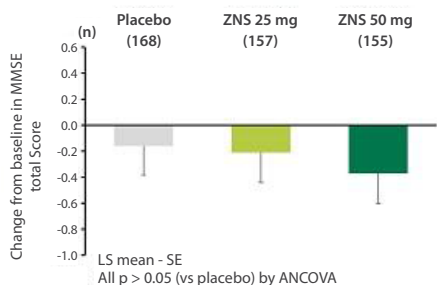
The responder proportions at W12 (LOCF) were 61.2%, 55.0%, and 37.6% for ZNS 25 mg, ZNS 50 mg, and placebo, respectively (figure 2).



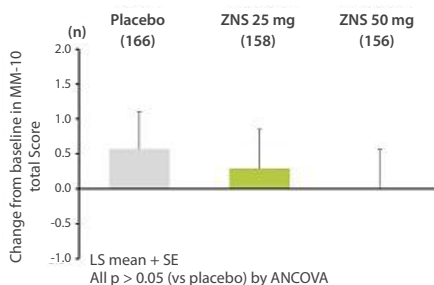
[Figure 2: Time course of responder proportion]

The changes in MMSE and NPI-10 total scores at W12 did not differ between ZNS (25 or 50 mg) and placebo (figure 3).

a) Change from baseline in MMSE total score at W12



b) Change from baseline in NPI-10 total score at W12



[Figure 3: Effect on cognitive function and BPSD]

The incidence proportion of adverse events did not significantly differ between ZNS and placebo, except for somnolence on ZNS 50 mg.

**Conclusions:** The analysis indicated that ZNS is effective for parkinsonism in DLB, particularly bradykinesia, tremor and rigidity, and is well tolerated.

P 154

## Disease course and treatment patterns in progressive supranuclear palsy: A real-world study

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**Objectives:** To understand the disease course of progressive supranuclear palsy (PSP) and how patients are currently managed in a real-world setting.

**Methods:** Data were drawn from the Adelphi Disease Specific Programme in PSP, a point-in-time patient-record-based study of neurologists and their PSP patients in the US, France, Germany, Italy, Spain & UK. Data were collected from July to November 2018.

The following outcomes from the physician-reported patient record form were included: symptom onset, symptoms that prompted initial consultation, symptoms that aided diagnosis, time from symptom-onset to diagnosis, time from diagnosis to use of mobility aids and care home, prior misdiagnoses, and currently prescribed treatment.

**Results:** The study included 203 neurologists and 892 PSP patients. 61% PSP patients were males with mean age of 68.9 years. Mean time from symptom-onset to diagnosis was about 15 months, with mean age at diagnosis being 67.3 years. Mean time from diagnosis to use of walking aid, wheelchair or care home was 9.9, 18.9 and 25.2 months, respectively. Among all the misdiagnoses, Parkinson's disease (67%) was the most common.

The most frequently reported symptoms that prompted initial consultation were difficulty walking/maintaining gait (54%), confusion (32%), loss of balance/falling and rigidity (both 30%). The most frequently reported symptoms that aided PSP diagnosis were difficulty walking/maintaining gait (49%), difficulty looking up (40%), difficulty looking down (34%), loss of balance/falling (33%) and rigidity (32%).

88% of patients were currently prescribed medication for their PSP symptoms, with Carbidopa/Levodopa being the most common medication (43%), followed by SSRIs/SNRIs (26%).

**Conclusions:** There is significant delay in diagnosing PSP. The time from symptom-onset to diagnosis may be an underestimate since the sample only included neurologists and no general practitioners. Understanding common symptoms that can differentiate PSP from other movement disorders can aid in reducing the time between symptom-onset and diagnosis.

P 155

## Normal pressure hydrocephalus in patient with multiple system atrophy: Innocent bystander or guilty party?

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**Background:** Normal pressure hydrocephalus (NPH) is a poorly understood condition, which typically presents with the triad of gait disturbance, urinary incontinence and cognitive decline. Diagnosis of NPH is often challenging due to its varied presentation and overlap with other neurodegenerative diseases including multiple system atrophy (MSA).

**Results:** A 68-year old male developed rapidly progressive gait difficulty, urinary incontinence and memory impairment. Neurologic examination showed parkinsonism on the right side and impaired postural reflexes. Brain MRI showed enlargement of the ventricles, narrowing of the high convexity cerebrospinal fluid (CSF) spaces with relative dilated Sylvian fissure, supporting features of NPH.

Further neuroimaging study of <sup>18</sup>F-fluorinated-N-3-fluoropropyl-2-b-carboxymethoxy-3-b-(4-iodophenyl) nortropine (<sup>18</sup>F-FP-CIT) positron emission tomography (PET) showed asymmetrically decreased FP-CIT binding in the left posterior putamen and <sup>18</sup>F-fluorodeoxyglucose PET showed decreased metabolism in the left basal ganglia, consistent with findings of MSA.

Although the patient's clinical symptoms of poorly levodopa responsive parkinsonism with autonomic failure and neuroimaging findings were consistent with MSA, there was a possibility that the patient's worsening gait, cognitive impairment, and urinary incontinence could be caused by coexisting NPH.

Therefore, the CSF removal was performed and the patient showed improvement in timed gait and cognitive function. After ventriculo-peritoneal shunt, his gait and cognition were improved.

**Conclusions:** NPH is a potentially treatable neurological disorder. Therefore it is necessary to consider the possibility of accompanying NPH when hydrocephalus is present in other neurodegenerative disease.

P 156

## Symptoms and burden of disease in patients with progressive supranuclear palsy

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**Objectives:** Progressive supranuclear palsy (PSP) is a rare, neuro-degenerative disorder with no approved treatment. This study aims to estimate the prevalence of PSP in the United States, explore PSP early symptoms and understand the economic burden associated with PSP.

**Methods:** PSP patients ( $\geq 2$  ICD-10 G23.1; or  $\geq 1$  ICD-10 G23.1 and  $\geq 1$  ICD-9 333.0) were identified from Medicare 100% Fee-For-Service Data from 1/1/2011 to 12/31/2017. The index date was defined as the first observed diagnosis date. Eligible patients had 12-month continuous enrollment pre- and post-index date.



The PSP cohort was matched 1:5 to a non-PSP cohort based on age, gender and index date. Prevalence was estimated for the year 2017 among Medicare enrollees. Symptoms before diagnosis were examined. Annual healthcare use and associated incremental costs were compared between the two groups.

**Results:** The study included 3,839 PSP patients with mean age of 75.4 years and 50.2% male. The age-standardized prevalence was estimated at 4.0% in 2017. Before diagnosis, main symptoms patients experienced related to PSP were abnormal gait (66.8%), falls (52.4%), fatigue (45.6%) and muscle weakness (40.0%). After diagnosis, 62.3% patients received levodopa-carbidopa for symptomatic treatment. Compared with non-PSP controls, PSP patients had higher annual healthcare utilization, specifically hospitalization rates (28.4% vs. 15.4%), post-acute care rates (47.5% vs. 11.5%), emergency department visit rates (49.2% vs. 12.1%), and more outpatient visits (15.6 vs. 11.0), all statistically significant at  $p < 0.001$ . PSP patients also had significantly higher total annual costs than non-PSP controls (\$43,405 vs. \$20,110,  $p < 0.001$ ), mainly attributable to higher medical costs.

**Conclusions:** The PSP prevalence was estimated based on diagnosed cases. Given diagnosis difficulty and sample limitations, the prevalence is likely an underestimate. PSP symptoms before diagnosis may provide meaningful insight to aid early diagnosis. PSP patients have significantly higher healthcare utilization and direct costs compared to non-PSP matched cohort.

## P 157

### A case report of notalgia paresthetica treated with pramipexole and clonazepam

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Notalgia paresthetica is a localized pruritus and dysesthesia syndrome on a small patch of the unilateral mid-back, usually between the shoulder blades, and typically confined to the dermatomes of T2-T6. The etiology of this condition is poorly understood, although recent correlation with degenerative spine changes suggests that spinal nerve impingement may be a contributing cause.

We report a case of 48-year-old man who suffered from notalgia paresthetica for more than 8 months, did not respond to treatment including local corticosteroid, imipramine, duloxetine, oxcarbazepine, pregabalin, or physical therapy, eventually reported alleviation of symptoms after taking pramipexole and clonazepam.

This condition raises the possibility that disorder of dopamine pathway may play a role in the etiology of notalgia paresthetica.

P 159

## Drug-induced parkinsonism may persist beyond two years after discontinuation of dopamine transmission blocking agents

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**Objectives:** To demonstrate that patients with drug-induced parkinsonism (DIP) can remain symptomatic beyond 6 months, what majority of literature suggests, after withdrawal of causative agents.

**Methods:** We report 2 cases of DIP followed longitudinally, with normal ioflupane iodine-123 (DaT) single-photon emission computed tomography (SPECT) scans.

**Results:** Our first patient developed acute onset rest and action tremors after beginning aripiprazole for depression. During our initial evaluation, he was diagnosed with DIP and switched to quetiapine, which has a lower risk of extrapyramidal symptoms, with marked improvement. Normal DaT scan was completed 16 months after switch of medications but with symptoms still present. Symptoms continued to improve but persisted at our last visit 27 months since discontinuation of aripiprazole but on quetiapine. Our second patient reports developing symptoms of parkinsonism 3 months after beginning risperidone and valproic acid for bipolar disorder.

About 57 months after symptom onset, patient discontinued all causative agents. DaT scan performed 8 months after discontinuation of all causative agents was normal despite continual parkinsonian symptoms. Our last visit, 22 months after discontinuation of all causative agents, revealed that the patient's symptoms were improving but still present.

**Conclusions:** Our cases demonstrate that symptoms of DIP can persist beyond the accepted 6 months since stopping the causative agents, and in our case beyond 22 and 27 months. Parkinsonism persisted at our last visit but improved during longitudinal follow-up, going against a progressive degenerative disorders such as Parkinson's disease. DaT scans showing normal dopamine transporters at 8 and 16 months since discontinuation of causative agents persuade us that the patients did not evolve or concurrently suffer from neurodegenerative causes of parkinsonism. An updated consensus regarding timeline for when to pursue other etiologies of parkinsonism in patients diagnosed with DIP after discontinuation of causative agents is needed.

P 162

## Approaches to the integrated management of parkinsonism syndrome in patients with chronic cerebral ischemia in Uzbekistan

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**Objectives:** Our aim was to evaluate the therapeutic efficacy of amantadine sulfate (in example of PK-Merz) in patients with secondary vascular manifestations of parkinsonism with chronic cerebral ischemia.

**Material and methods:** In total 30 patients were researched, including 14 males (46.6%) and 16 females (53.3%) with secondary vascular parkinsonism (VP) with chronic cerebral ischemia (CCI). The age of patients ranged from 58 to 72 years (mean age  $61,5 \pm 4,8$  years). All patients, along with basic therapy, was prescribed PK Merz (active substance amantadine sulfate 100 mg). During the first 5 days of a drug administered in infusion of 200 mg 1 time per day for 3 hours (infusion rate - 55 drops per minute). The duration of treatment was 30 days. Cerebral hemodynamics was studied using ultrasound transcranial Doppler.

**Results:** The majority of patients after completion of treatment marked improvement of a night's sleep, increase efficiency. The most significant change noted in improving memory, reduce anxiety and improve mood, headache and dizziness ( $p < 0.05$ ). As a result of treatment, memory and the number of reproduced words in the test "10 words" were improved ( $p < 0.05$ ), there was a decrease of perseveration and contamination. Marked improvement in mental performance and concentration was occurred, which is reflected in a decrease of the average time in performing the sample of Schulte ( $p < 0.05$ ). Dynamics of the total cognitive defect on the MMSE in the studied patients in the treatment process has been positive ( $p > 0.05$ ).

**Conclusions:** PK-Merz on the background of complex treatment of patients has a positive therapeutic effect, which manifests itself in smoothing light and mild cognitive impairment, a decrease of brain and asthenic-depressive symptoms. There was revealed moderate antidyskinetic positive effect of the drug PK Merz.

P 163

## Oculomotor impairment in atypical parkinsonian disorders: Corticobasal degeneration and progressive supranuclear palsy

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**Objectives:** This study sought to ascertain the value of clinical examination of eye movements in differentially diagnosing corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP) and identify hallmark oculomotor deficits associated with the two disorders.

**Methods:** Clinician review data for the project were obtained from a total of 134 patients recruited to PROSPECT, a UK-wide study seeking to characterise disease progression in CBS, PSP and multiple system atrophy. 14 patients that fulfilled neither Armstrong criteria for CBS nor the Movement Disorders Society

criteria for PSP were diagnosed as having an 'atypical parkinsonian syndrome' (APS) and included as a comparison group. Clinician reviews were performed by participating neurologists at several UK sites: oculomotor analysis was based on the standardised protocol for assessment of eye movements in PSP, as set out in the PSP rating scale. Saccadic velocity/hypometria was assessed in the upward, downward and horizontal directions. Saccadic latency not being assessed at the time of clinician review, this was categorised retrospectively using video recordings made of the examinations of 29 patients, using an ordinal scale of 0-3 devised for this project.

**Results:** Velocity/hypometria score for saccades in all directions was greater in PSP patients ( $p < 0.01$ ) than CBS and APS. Velocity/hypometria score for saccades in the upward direction was greater in both PSP and CBS compared to APS ( $p < 0.01$ ); for both downward and horizontal saccades, velocity/hypometria was not significantly different to the APS group ( $p > 0.05$ ). Latency of horizontal saccades was most affected in the CBS group compared to PSP and APS ( $p < 0.01$ ).

**Conclusions:** Clinical assessment of eye movements can assist with the differential diagnosis of CBS and PSP. Further study using objective measures of oculomotricity, such as infrared eye tracking, would enable quantification of oculomotor deficit in this disorders.

## P 164

### Assessment of psychosis in patients with Parkinson's disease

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**Background and aims:** Psychosis plays an important role among patients diagnosed with Parkinson's disease. It is believed that unto 70% of PD patients are affected with psychosis. Although many different hallucinations, illusions, and delusions are reported in PD, the majority of episodes are visual hallucinations. To better quantify PD psychosis and aid in future therapeutic trials, our study aims to designed a PD specific psychosis scale and undertook psychometric evaluations in order to rule out psychosis associated with PD.

**Materials and methods:** A cross sectional study was conducted in Sir GangaRam Hospital Lahore during May 2017 to August 2018. Total 80 patients diagnosed with Parkinsonism syndrome were included in the study. A questionnaire was established. The first five questions identify the type of hallucination (visual, auditory, olfactory, sense of presence) or delusion while the second five questions further quantify the intensity, frequency, insight and impact of the worst psychotic feature on the life of the patient and family. Analyses were performed using SAS 9.3.

**Results:** Sixty different PD patients with psychosis and 20 PD patients without psychosis were included in the study. In psychosis subjects, results were normally distributed: mean 19.23. In those without psychosis 12 % scored  $> 0$ . The intra-rater, inter-class correlation coefficient was excellent ( $N = 28$  pairs of observations seven days apart,  $ICC = 0.87$ ). Inter-rater reliability (two different raters,  $N = 48$  pairs) was outstanding for the entire group,  $ICC = 0.92$ ). As expected visual hallucinations were most common (mean = 4.19). The presence of delusions was associated with greater total scores.

**Conclusions:** We report very good intra-rater reliability and excellent inter-rater reliability on a 10 question scale designed specifically for PD associated psychosis.

P 165

## **Parkinsonism secondary to mercury poisoning in a Colombian population**

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Parkinsonism refers to a group of neurological movement disorders similar to those seen in Parkinson's disease (PD); characterized by bradykinesia, muscle rigidity and resting tremor. Mercury is a heavy metal and its compounds are recognized as potentially hazardous materials. Industrial growth, and especially fluorescent lamps, has increased exposure and the risk of mercury poisoning. Through environmental and case-control studies, it has been shown that mercury is related to the presence of parkinsonism.

A descriptive observational study of patients diagnosed with mercury poisoning and secondary parkinsonism, in a Neurology clinic of the University Hospital between 2015-2016. Sociodemographic, clinical and laboratory variables are described, collected in each patient. A total of 7 individuals were reported in whom there is evidence of mercury poisoning secondary to occupational exposure and that after the chelation and management of the acute symptoms present parkinsonism. Of the individuals studied, 100% were male and belonged to a company that produces fluorescent lamps.

## Topic: Hyperkinetic movement disorders: Ataxias, Tics and Myoclonus

P 166

### Sequencing of microRNAs in blood of SCA2 patients reveals hsa-miR-451 as potential target

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**Background and Objectives:** Beyond specific threshold level, (CAG) triplet repeats make a toxic gain of functional protein and which results in neurodegenerative disorders like spinocerebellar ataxia type-2. MicroRNAs (miRNAs) are well known to modulate several disease phenotypes. We investigated blood PBMCs using Next Generation Sequencing (NGS) aiming to find some targetable miRNAs.

**Methods:** NGS of RNA samples (RIN $\geq$ 8) of genetically confirmed SCA-2 patients (n=7) and matched healthy individuals (n=7) was done on Illumina HiSeq-2500 platform. After removing adapters, the sequence was aligned using mirDeep-2 and differential expression was calculated using DESeq2. The miR-TargetLink web-tool was used to identify target genes. The gene ontology (GO) database and KEGG pathway databases were used to perform GO functional and pathway enrichment analyses, respectively.

**Results:** Out of 548 differentially expressed miRNAs identified, we found two up-regulated (hsa-mir-222, hsa-mir-134) and three down-regulated (hsa-mir-451, hsa-mir-183, hsa-mir-374) having FC $\geq$ 1.5 and p<0.05. Low levels of mir-183, mir-451, mir-374 are corroborated in PI3K-Akt signaling pathway, mTOR signaling pathway and MAPK signaling pathways. Low levels of miR-451 had shown neurotrophic, neuroprotective anti-oxidant, and anti-apoptotic effects. Down-regulation of hsa-miR-451 was also shown in leukocytes from Italian ALS patients. The targets of miR-451 includes genes like MMP2, MMP9, BCL2, PKD1, MYC, RAB5A and IL6R which are involved in different disease related pathways. The miR-134 is brain-specific and known to be actively involved in the regulation of neuronal microstructure. High levels of this miRNA in blood needs more investigation.

**Conclusions:** Out of all identified miRNAs, hsa-miR-451 is a nodal miRNA which is involved in several different pathways and steps related to SCA2 pathophysiology. Further investigation on levels of its target genes in related pathways will strengthen its role as potential biomarker or therapeutic target. Analyzing the role of brain specific mir-134 in SCA2 patients will also reveal new pathways in disease pathophysiology.

P 167

## Correlation of CAG repeat with autonomic function in spinocerebellar Ataxia Type-2 (SCA-2)

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**Objectives:** To explore association of expanded CAG repeat with autonomic function in SCA2 patients.

**Background:** SCA2 is a progressive neurodegenerative disorder characterized by gait, limb ataxia and autonomic dysfunction. It is an autosomal dominant disease caused due to expansion of trinucleotide CAG repeats in *ATXN2*.

**Methods:** Genetically confirmed 72 SCA2 patients were recruited from Ataxia clinic, AIIMS. All the patients underwent detailed clinical evaluation, radiological, biochemical and electrophysiological testing. They underwent detailed autonomic function testing including a) Deep breathing test b) Valsalva maneuver test c) Isometric exercised d) Cold pressor test and e) Postural tests. Autonomic function was considered as abnormal if any of the above testing domains were abnormal. Their autonomic functions were correlated with their genetic spectrum.

**Results:** Total 72 unrelated SCA2 patients (42 Male and 30 females) had mean (SD) expanded trinucleotide repeats of 41.5(±2.69) with a range of 36-49. Autonomic function parameters were abnormal in 56 (77.77%) with expanded CAG range of 37-49 repeat and normal 16(22.22%) with expanded CAG range 36-48 repeats. In patients with normal Autonomic function, mean (SD), range of age at onset was 29.03(11.97), 17-46 and mean (SD), of CAG repeat is 42.75(3.47). In patients with abnormal Autonomic function, mean (SD), range of age at onset is 31.69 (9.72), 10-55 and mean (SD), of CAG repeat is 41.12(2.64). No significance difference has been observed in these two group.

**Conclusions:** SCA2, the commonest spinocerebellar ataxia in India shows great clinico-genetic heterogeneity. Our study shows that number of Trinucleotide repeats (TNR) may not be causal for abnormal autonomic function in SCA2 patients.

P 168

**Neurofascin gene (NFASC) mutation causes autosomal recessive ataxia with demyelinating neuropathy**

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**Objectives:** To find the genetic cause of early onset cerebellar ataxia and demyelinating neuropathy in two siblings from a consanguineous Italian family.

**Methods:** A combined approach of linkage analysis and whole-exome sequencing was performed to find the causative mutation. Functional studies were conducted on neurons from induced pluripotent stem cells (iPSCs) generated from the patients.

**Results:** Genetic analysis revealed a homozygous p.V1122E mutation in Neurofascin gene (*NFASC*). This mutation, affecting a highly conserved hydrophobic transmembrane domain residue, led to significant loss of Neurofascin protein in the iPSC-derived neurons of affected siblings.

**Conclusions:** Neurofascin is a transmembrane protein that plays an essential role in nervous system development and node of Ranvier function. Anti-Neurofascin autoantibodies cause a specific type of chronic inflammatory demyelinating polyneuropathy (CIDP) often characterized by cerebellar ataxia and tremor. The identification of *NFASC* mutations paves the way for genetic research in the developing field of nodopathies, an emerging pathological entity involving the nodes of Ranvier, which are associated for the first time with a hereditary ataxia syndrome with neuropathy.



## Topic: Hyperkinetic movement disorders: Chorea, Tremor and other

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### Importance of the initial response to GPi deep brain stimulation in isolated dystonia: A nine year quality of life study

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**Objectives:** Long-term efficacy of deep brain stimulation (DBS) on quality-of-life (QOL) for isolated dystonia is not well established. This study aims to determine the long-term impact of DBS on QOL outcomes and identify clinical predictors.

**Methods:** We retrospectively investigated 16 inherited or idiopathic isolated dystonia patients treated with bilateral globus pallidus internus DBS who were followed beyond 9 years at our center. The cohort consisted of 9 males, 7 females; 10 generalized, 6 segmental; mean (range) age at implantation, 37.0 (8-67) years; mean follow-up duration after implantation, 10.9 (9-13) years. We employed the Unified Dystonia Rating Scale for motor and Short Form Health Survey for QOL assessments to monitor the change longitudinally. We analyzed the changes in motor and QOL at 1-2 years (short-term) and  $\geq 9$  years (long-term) follow-up as compared to baseline with a Wilcoxon signed-rank test. We assessed the factors that predicted motor and QOL improvement with univariate regression analyses.

**Results:** Motor (41.6%;  $p = 0.004$ ) and QOL (total score,  $p = 0.039$ ) improvements remained significant at long-term follow-up and, in the regression analysis, change in QOL outcomes correlated significantly with change in motor outcomes ( $R^2 = 0.384$ ,  $p = 0.010$ ). Additionally, short-term motor and QOL improvements predicted the long-term motor ( $R^2 = 0.384$ ,  $p = 0.010$ ) and QOL (total score,  $R^2 = 0.594$ ,  $p < 0.001$ ) outcomes, respectively.

**Conclusions:** Motor and QOL improvements with DBS in isolated dystonia remain sustained for nearly a decade and may largely be predictable by the short-term response to DBS.

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## Huntington's disease: Cognitive correlations of defective emotional recognition

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**Objectives:** Deficient recognition of facial emotional expressions occurs in Huntington's disease (HD). We aimed to figure out which cognitive dysfunctions correlated to poor emotional recognition in HD.

**Methods:** HD patients were investigated for facial emotional recognition through Ekman Pictures of Facial Affect (EPFA). A full neuropsychological battery and clinical scales were applied to all participants. Also, we seek for CAG repetitions and CAP score correlations.

**Results:** Thirty-four HD patients were studied (61.8% female). Age ranged 19 to 63 y-old, and mean age was 45.7 (SD = 12.8). Age at onset ranged 14 to 61 y-old. Mean disease duration was 5.9 years (SD = 5.5). Mean CAG repetitions was 47.2 (SD = 10.3), and mean CAP score was 98.7 (SD = 17.2). There were no correlations between EPFA global score with age, schooling, sex, age at onset, disease duration, number of CAG repetitions, or CAP score.

There was a positive correlation with Unified HD rating scale - functional, independence and incapacity scores ( $Rho = 0.46; 0.67; 0.56$  -  $p = 0.038; p < 0.001; p < 0.01$ , respectively). EPFA global score significantly correlated to Dementia Rating Scale (Mattis) to the total score, and subscores on attention, perseveration, and constructional. We also found a significant correlation between EPFA score with attention and executive functions tests performance (verbal fluency, Stroop test, Digit Span, Symbol Digit Modalities Test, and Frontal Battery Assessment). EPFA global score did not correlate to semantic and verbal memory tests performance, but there was a mild correlation to visual memory retention ( $Rho = 0.47; p = 0.024$ ).

A multivariate regression analysis disclosed executive dysfunction as a predictor of poor emotional recognition.

**Conclusions:** Defective emotional recognition is related to executive dysfunction in HD and is predictive of poor independence and high functional incapacity.

## Successful living kidney donation in a patient with Huntington's disease

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**Objectives:** To report on a Huntington's Disease (HD) patient who underwent living kidney donation and examine the decision-making process and ethical considerations.

**Background:** HD is an autosomal dominant, incurable, neurodegenerative disease with motor, cognitive, and psychiatric symptoms. According to UNOS, approximately 95,000 people within the United States await kidney donor, and many will die before receiving a new kidney. There are currently no published ethical or medical guidelines regarding kidney donation in persons with HD.

**Methods:** A 46-year old Caucasian male with 6 years of clinically manifest and genetically confirmed HD wished to donate his kidney to an unnamed recipient. He first expressed interest in altruistic kidney donation with the thought that "he wanted to help others." His clinical exam revealed moderate chorea, mildly impaired cognitive functions, and normal psychological functions. Discussions between the HD and transplant teams ensued as literature regarding this in HD is scant. Our patient underwent full neuropsychological testing revealing mild deficits in executive functions, recent memory, and visual perception. After completing prerequisite testing (i.e., laboratory and urine tests, ECG, chest x-ray, and CTA abdomen and pelvis, and neuropsychological testing) by the HD and transplant teams, he was deemed eligible for kidney donation. He underwent laparoscopic left-sided nephrectomy 16 months after first inquiry.

**Results:** He tolerated the procedure well and had an excellent post-operative course. Follow up visit one week post-op revealed discontinuation of pain medications and resumption of biking for transportation. His HD symptoms remained stable throughout hospitalization and post-operative course.

**Conclusions:** After undergoing the appropriate neurological, neuropsychological, and medical screening and pre-operative work-up, we believe a diagnosis of HD is not an absolute contraindication for kidney donation. A team approach and communication between the HD and transplant teams are essential. Decision-making capabilities, cognitive status, comorbid conditions, and support system must be taken into account.

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**Suicide in neuroacanthocytosis: Are clinicians aware enough?**M. Gultekin<sup>1</sup>*<sup>1</sup>Erciyes University Faculty of Medicine, Department of Neurology, Kayseri, Turkey*

**Background and aims:** Chorea-acanthocytosis (ChAc) is very rarely seen and it is one of progressive neurodegenerative disorders. Unfortunately, life expectancy is short for these patients. Different causes of death could be in ChAc. Some patients' death may be due to suicide. Identifying causes of mortality is important for disease management and following the patients. This case series is written to emphasize suicide among the patients with ChAc.

**Methods:** A family consisting of parents and 9 siblings: Four members of the family (two female, ages 31, 36 and two male ages 44, 49) have ChAc. Confirmation of the diagnosis of ChAc was done as molecularly confirmed based on Western blot. Neurological examination of all of these patients revealed severe chorea, gait instability, and dysarthria. There were seen lesions due to biting on his lips, oral mucosa, and tongue.

**Results:** In the following time, after several years, two of these patients were learned that (age 36, female and age 49, male) had died due to suicide (hanged). Then, the others were bedridden because of the disease progression.

**Conclusions:** Cause of death in ChAc as suicide was not rare. Clinicians should be aware of that. They should focus upon disease management and treating symptoms which may contribute to mortality.

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**Demyelination-related movement disorders: Prospective evaluation of 152 patients and comparative analysis of patients with and without spinal lesions**H. Abboud<sup>1</sup>, H. Khan<sup>1</sup>, K. Knusel<sup>1</sup>, X.X. Yu<sup>2</sup>, J. Cohen<sup>3</sup>, H. Fernandez<sup>2</sup>

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**Objectives:** To compare demyelination-related movement disorders in patients with and without spinal lesions.

**Methods:** Pooled analysis of two prospective cohorts with demyelinating diseases. Each patient answered a movement disorder survey and was clinically evaluated by a movement disorder specialist. Patients were stratified into two groups according to the presence or absence of spinal lesions and phenomenology was compared between the two groups using the chi square test. Patients with ganglionic lesions were excluded. Only movement disorders with probable spinal origin according to previously published criteria were included in patients with spinal lesions. Movement disorders with possible mixed origin were excluded from this group to increase confidence in the spinal origin of these involuntary movements.

**Results:** A total of 152 patients were included (mean age 43.9 years, 63.4% female, 95.4% with multiple sclerosis). There were 93 patients with spinal lesions and 59 without. The most common demyelination-related movement disorders in the entire cohort in a descending order were: tonic spasms, tremor, sec-

ondary restless leg syndrome (RLS), myoclonus, focal dystonia, fasciculations, spontaneous clonus, and hyperkeplexia. After excluding movement disorders with possible mixed origin from the spinal group, the following movement disorders remained more significantly prevalent in patients with spinal lesions than those without spinal lesions: tonic spasms ( $P=0.013$ ), RLS ( $P=0.0001$ ), and spontaneous clonus ( $P=0.016$ ). Tremor was significantly more prevalent in patients without spinal lesions ( $P=0.032$ ) while dystonia, myoclonus, fasciculations, and hyperkeplexia showed no statistical difference in distribution between the two groups.

**Conclusions:** Central demyelination can result in a variety of movement disorders. Tonic spasms, secondary RLS, and spontaneous clonus are strongly-linked to spinal generators while tremor is often supraspinal in origin. Other movement disorders result nearly equally from spinal or supraspial demyelination.

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### Orthostatic tremor - clinicopathological report

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**Objectives:** Clinical and pathological findings of a 95 year old male with orthostatic tremor that came to autopsy.

**Methods:** In his mid-20's his legs would tremor with prolonged standing in the shower. At age 50, co-workers commented that he would sit or lean when not walking. His symptoms remained mild in his mid 60's. By age 75 he had problems standing still; his legs would shake and he would have to move. At age 94 he was seen by Psychiatry and Geriatrics. Electrodiagnostic studies were consistent with a length dependent sensorimotor neuropathy with no evidence of active denervation. Multidisciplinary evaluation revealed mild dementia (MMSE 26/30). Reversible causes of his symptoms were excluded (including B12, thyroid, diabetes). Head CT revealed mild generalized atrophy, mild microvascular ischemic changes, and a remote infarct of the right caudate. He had very good static and dynamic sitting balance but very poor static standing balance, and no loss of balance or unsteadiness when using his four wheeled walker.

**Results:** Neurological evaluation at age 95 revealed decreased vibration and pinprick in the lower limbs. He had slight postural tremor but no ataxia. Tone was normal and there was no bradykinesia or resting tremor. After standing for 3 to 5 seconds, his legs would shake and he needed to sit or to move; he did not develop these symptoms if allowed to walk. Posture was flexed and he had a shuffling gait with short, rapid steps. He was video recorded during gait and EMG which revealed 10-15 Hz tremor in the gastrocnemius when standing (but not seated); he died within 2 months of that assessment. Brain autopsy showed Alzheimer-type changes and vascular disease; spinal cord was unremarkable.

**Conclusions:** This is the first autopsy reported case of orthostatic tremor. No specific pathological findings were noted.

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**Orthostatic jaw tremor: A diagnostic challenge**

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**Objectives:** Jaw tremor is a component of various neurological disorders and. Isolated jaw tremor is a rare clinical presentation. We aimed to present a rare movement disorder of an orthostatic jaw tremor and a remarkable benefit from treatment with botulinum toxin A.

**Methods:** Case report.

**Results:** We present a 40-y man with a 3-year history of jaw tremor, no other neurological symptoms or a family history of neurological disorders. The tremor was paroxysmal, lasting minutes to hours. It was never present during sleep, and he could make it stop by making any movement with his mouth. The movements were not affected by consuming alcohol and did not affect the voice or the swallowing. On examination, we noticed a rapid rhythmic movement of the relaxed jaw. It disappeared when he opened his mouth, spoke, clenched his teeth or any additional voluntary movements that required activation of the masseters. It recurred immediately upon returning the jaw to a resting position. The movement did not change in frequency or amplitude with distraction maneuvers. The remainder of the neurological examination was normal. He had undergone an extensive unrevealing workup including a contrast-enhanced brain magnetic resonance imaging. The needle electromyography examination showed involuntary, intermittent and synchronized muscular contractions in both masseter muscles, at a frequency of 14 Hz. No changes were found in other muscles. We treated him by injecting 25 units of botulinum toxin type A into each masseter. The tremor completely disappearing five days after the injections and was no longer detectable by electromyography.

**Conclusions:** The frequency of most types of jaw tremor is lower than 12 Hz and it is usually associated with other abnormal involuntary movements. We presented a rare case of jaw tremor with neurophysiological characteristics of primary orthostatic tremor. There was a striking response to botulinum toxin.

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**Coexistence of Huntington's disease and brain tumors - a single center experience**

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**Objectives:** To describe the clinical presentation and diagnostic findings in three patients with Huntington's disease (HD) who were also found to have brain tumors.

**Background:** Various studies have shown that there is a lower incidence of cancers in patients with HD. Only a single case report in 1996 has previously described coexistence of Huntington's disease with a brain tumor.

**Design and Methods:** Case series and review of literature.

**Results:** Of the three patients, two were female (patient A and B) and one male (patient C). All three had genetically confirmed HD and were manifest HD. Patient A's total functional scale (TFC) was stage I. She presented with both hypomotor and hypermotor seizures in the absence of any focal neurologic signs. Imaging revealed an expansile non-enhancing right inferior temporal lesion. She underwent surgical resection for the same with confirmed tissue diagnosis of dysembryoblastic neuroepithelial tumor. Patients B and C were in TFC stage III-IV. Both were noted to have new-onset hypermotor seizures and focal cortical signs (apraxia and visual neglect respectively) which led to further clinical evaluation and radio-imaging which revealed diffusely infiltrative intracranial tumors suggestive of high-grade gliomas. Patient B underwent surgical resection with a confirmed tissue-diagnosis of glioblastoma multiforme (GBM). Patient C's tumor was more aggressive and not amenable to resection.

**Conclusions:** Neuropsychiatric manifestations of HD often mask concurrent neuro-pathologies and confound their diagnosis. Longitudinal comprehensive care is helpful in raising clinical suspicion for a non-HD cause given new focal neurologic symptoms which are typically not a part of the HD clinical spectrum. In addition, while seizures can be seen in juvenile HD patients, adult-onset seizures in this population warrant a thorough investigation to rule out structural causes such as intracranial masses. Diagnosing brain tumors in this population while challenging does impact their therapeutic options and clinical course.

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### Heart rate variability and the risk of falling in Huntington's disease (HD)

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**Objectives:** To evaluate the relationship between the HRV and the risk of falling in HD patients.

**Methods:** Eighteen HD patients were assessed by short-term HRV analysis EKG were recorded during 5 minutes in resting and standing states. Time and frequency domains, and non-linear parameters were calculated. Data in each state and its difference between were analyzed. Additionally, data regarding falls, measurements of the risk of falling [Berg balance Scale (BBS), Timed-up go test (TUG) and Tinetti mobility test (TMT)] were collected.

**Results:** The prevalence of falls was 38.9% reporting at least one or no one fall (single faller) and 61.1% reporting two or more falls (recurrent fallers). There was no difference in age, gender, illness duration, number of CAG repetitions, total motor score (UHDRS-TMS), functional capacity (UHDRS-TFC) or any scale of risk of falling between groups. Recurrent fallers had significantly lower RMSSD in resting state ( $p=0.020$ ), higher LF/HF ratio in both states (resting,  $p=0.011$ ; standing,  $p=0.044$ ) and higher DFA  $\alpha 1$  in both states (resting,  $p=0.027$ ; standing,  $p=0.011$ ). Patients classified with high risk of falling by BBS in resting state showed higher power of low frequency ( $p=0.044$ ) and higher DFA  $\alpha 2$  ( $p=0.011$ ). Correlations were found in resting state between the RMSSD and [number of falls ( $r=-0.486$ ,  $p=0.041$ ), UHDRS-TMS ( $r=-0.408$ ,  $p=0.030$ ), BBS ( $r=0.049$ ,  $p=0.470$ )] and LF/HF ratio and number of falls ( $r=0.539$ ,  $p=0.021$ )). No significant differences were found between recurrent and single fallers for any blood pressure measures.

**Conclusions:** The observed HRV pattern is consistent with a higher sympathetic prevalence associated with a higher risk of falls. The short-term HRV assessment is a useful and rapid tool to assess the risk of falling in HD. The decrease of parasympathetic HRV values adequately identifies the high risk of falling, independently of orthostatic phenomena in HD.



## Topic: Dystonia

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### Precise classification and related responsible muscles of cervical dystonia

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**Objectives:** To analyze the precise classification of cervical dystonia (CD), the distribution of responsible muscles for each subtype and the improvement of symptoms after botulinum toxin (BTX) injection.

**Methods:** Clinical data of CD patients treated with BTX between March 2010 and March 2017 in Shanghai Tongji Hospital were assessed by the col-cap concept (laterocaput, laterocollis, torticaput, torticollis, anterocaput, anterocollis, retrocaput, retrocollis, sagittal shift forwards, lateral shift, sagittal shift backwards). The responsible muscles according to EMG of each patient, as well as their symptom relief after BTX injection (evaluated by Tsui score) were analyzed.

**Results:** A total of 207 CD patients (88 males and 119 females) with 451 treatments were included. Among them, 255 cases were single col-cap subtype, 163 cases were combination of two subtypes, 21 cases were combination of three subtypes, and 12 cases were head tremor subtype. In single col-cap subtype, torticaput is the most common (23.92%), followed by torticollis (12.30%). Sagittal shift forwards (0.68%) and lateral shift (0.23%) are the less common. In complex subtypes (combination of two or three subtypes), torticaput combined with torticollis is the most common (28.26%), followed by torticaput combined with laterocaput (19.02%). A total of 165 patients completed video follow-up, Tsui scores were significantly reduces after BTX treatment in torticollis, torticaput, laterocollis, laterocaput and retrocaput. In rotation and lateral flexion subtypes, common responsible dystonic muscles include sternocleidomastoid, trapezius, splenius capitis, semispinalis capitis, levator scapulae and scalenus. Torticaput subtype may also involve obliquus capitis inferior, and torticollis subtype may involve splenius cervicis.

**Conclusions:** In single col-cap subtype, torticaput is the most common, followed by torticollis. In complex subtypes, torticaput combined with torticollis is the most common, followed by torticaput combined with laterocaput. In all 11 subtypes, torticollis, torticaput, laterocollis, laterocaput and retrocaput have better therapeutic effect with BTX.

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**Bilateral ptosis and laryngeal dystonia induced by chlorpromazine**W.T. Yoon<sup>1</sup>*<sup>1</sup>Sungkyunkwan University School of Medicine, Kangbuk Samsung Hospital, Neurology, Seoul, Republic of Korea*

**Objectives:** Bilateral ptosis or laryngeal dystonia may occur due to various etiologies including some drugs, respectively. But, chlorpromazine induced bilateral ptosis and laryngeal dystonia is not reported in the literature. Our aim is to report unusual case of man who developed prominent bilateral ptosis and laryngeal dystonia induced by chlorpromazine.

**Methods:** Single case report and description of clinical characteristics.

**Results:** A 72-year-old korean man was referred to our neurologic department due to involuntary movements presenting irregular bilateral ptosis, intermittent problems of vocalization and dysphonia. He presented relatively subacute-onset bilateral ptosis and repetitive dystonic movements of oropharyngeal muscles two days ago. His dystonic symptoms of vocalization and dysphonia had more aggravated in long-time speech, and he had intermittent shortness of breath, as like inspiratory stridor.

Other neurological examination, brain imaging and electrophysiological tests were normal. After chlorpromazine was discontinued, his dystonic symptoms gradually improved and completely resolved two weeks later.

**Conclusions:** To our knowledge, this is the first case report of prominent bilateral ptosis and laryngeal dystonia induced by chlorpromazine. As like this case, if there is acute or subacute-onset, not-fixed, continual bilateral ptosis and laryngeal dystonia with psychiatric medications, it should be considered diagnosis of drug-induced bilateral ptosis and laryngeal dystonia.

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**Fluoxetine Induced reversal of levodopa benefit in one patient with dopa-responsive dystonia**M. Gultekin<sup>1</sup>*<sup>1</sup>Erciyes University Faculty of Medicine, Department of Neurology, Kayseri, Turkey*

There have been numerous reports of SSRIs, when used alone or in combination with other antipsychotics, inducing movement disorders. Fluoxetine is the first SSRI in the market. This class of drugs is used to treat depression, anxiety, and other mood disorders.

A 38-year-old woman who had been using levodopa 62.5 mg due to dopamine-responsive dystonia since the age of 12. Also, she was using escitalopram for over 6 years due to depression. Escitalopram is planned to start by cutting fluoxetine to prevent weight gain in the patient. Ten days after the onset of fluoxetine, contraction began in the bilateral proximal lower extremities of the patient. Levodopa daily dose rose to 187,5 mg but the patient's complaints did not decrease. The patient also, had complaints such as restlessness, insomnia, drowsiness, and inability to sit for a long time. the patient applied to the emergency service with these complaints. The patient was given diazepam 10 mg and there was a short-term improvement in the

patient's complaints. Zopiclone and medazepam added to the patient's treatment for restlessness and insomnia for her complaints. The patient's fluoxetine was discontinued on the 18th day of treatment and after that the patient's contractions are reduced. Then, she had recovery and no any problem. This is the second report of fluoxetine making the symptoms of dopa-responsive dystonia reappear by reversing the benefit of levodopa.

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## **To seize or not to seize: The evaluation of dystonic tremor on video EEG**

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**Objectives:** To describe the case of an 82-year-old female with a history of suspected post-stroke epilepsy found to have a combination of essential tremor and dystonic tremor.

**Methods:** An 82-year-old woman with a past medical history of lacunar left globus pallidus infarct and a large right middle cerebral artery (MCA) infarct with presumed post-stroke epilepsy (on levetiracetam), was admitted for suspected breakthrough seizures. Valproic acid and phenytoin were added given refractory "seizures" and she was transferred to our center. Video EEG (vEEG) monitoring was initiated and multiple presumed focal electrographic seizures lasting 15-60 seconds were captured, characterized by development of rhythmic sharp waves over the left temporal lobes. There was no response to anti-epileptic drugs (AEDs). However, the clinical correlate was high-amplitude 4-5 Hz rhythmic shaking of the head without any disturbance of language, consciousness, or cognition. Tremor was exacerbated by straightening and turning her head to the left side. At rest, the patient had torticollis and laterocollis to the right with hypertrophy of the left and right sternocleidomastoids, right splenius capitis, and right trapezius with pain on palpation, suggestive of dystonia and dystonic tremor. At baseline she also had features of essential tremor.

**Results:** In this case, vEEG was both misleading and diagnostic. The episodes captured seemed to demonstrate a focal seizure, but after closer examination, were consistent with ipsilateral motion artifact from the rhythmic movement of the head and neck. Supporting this was lack of response to AEDs, physical exam with dystonic features exacerbated by antagonistic movement, and hypertrophy of the corresponding muscles suggestive of dystonia and dystonic tremor. Furthermore, the patient was started on clonazepam and propranolol with significant improvement.

**Conclusions:** The distinction between movement disorders and seizures can be difficult to ascertain, but vEEG can be useful for differentiation.

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## Embouchure dystonia

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Focal task-specific dystonia (FTSD) is a focal dystonia that occurs only when performing a specific task. While the most common form of FTSDs is writer's cramp, FTSDs can also be seen in professionals such as musicians and tailors. FTSDs in musicians are usually observed in musicians who play the string instruments such as guitar and violin. However, FTSDs in musicians playing wind instruments are very rare; and this type of dystonia is called Embouchure dystonia. We report a professional saxophone player with embouchure dystonia.

A 24-year-old woman complaining of difficulty in playing her instrument and involuntary contractions around her mouth while performing for 3 weeks was admitted to our clinic. The patient's routine neurological examination was normal. While the patient was performing, involuntary contractions of depressor anguli oris and risorius muscles were observed by means of physical examination and a surface electromyographic study. Brain MRI for ruling out the secondary causes revealed no abnormality. The patient was started on clonazepam treatment and was followed-up for the treatment response.

Embouchure dystonia is a very rare entity in daily neurology practice and should be considered in people who play wind instruments. The mechanism of embouchure dystonia and which musicians carry the risk for embouchure dystonia development are not clear. The current literature supports the use of agents such as anticholinergics, benzodiazepines and botulinum toxin therapy as treatment options.

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## High dose botulinum toxin therapy: Safety, benefit and endurance of efficacy

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**Objectives:** To assess safety, therapeutic response and long-term benefit of higher dose Onabotulinum toxin A (OnaA).

**Background:** Botulinum toxin therapy is a powerful tool for treating many neurologic disorders. The US FDA-approved maximum OnaA dose is 400 units (U) per visit. While in practice higher doses are commonly used, safety and long-term benefit are not well reported.

**Methods:** We used the prospective University of Florida INFORM database and chart review to identify patients treated with OnaA above 400U/visit.

We collected demographics, OnaA dose, body regions injected, patient-reported efficacy via 7-point Clinical Global Impression Scale (CGIS) and duration of benefit. Safety was determined by reported side effects at first follow-up from >400U visit. We assessed longer-term outcomes at 6 months, 12 months and last follow-up.

**Results:** We identified 68 patients [43 female (63%); mean age 60yo (range 24-87)] who received OnaA above 400U/session. Mean total dose was 501U (range 425-800). 43 patients were injected for dystonia; 6 had blepharospasm, 31 cervical, 2 truncal, 14 upper limb and 14 lower limb dystonia (20 had >1 region injected). 25 patients were injected for spasticity; 18 upper limb, 16 lower (9 had both). More than 70% of patients self-reported “very much improved” or “much improved” at 6 month, 1 year and last visit. Mean duration of benefit was 9 weeks (SD 3). Ten patients (15%) reported adverse effects (AEs) at first follow-up, of which 3 had more than 1 AE [weakness (n=3), head drop (n=3), bruising (n=3), dysphagia (n=2)]. At last visit, 9 patients decreased dose below 400U, and 36 patients discontinued injections at our center; reasons included lost to follow-up/moved (n=19), death/hospice (n=7), lack of benefit (n=5) and AEs (n=2).

**Conclusions:** OnaA doses greater than 400U may be safe and effective in appropriate patients.

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### Addressing anxiety and mood disorders in dystonia

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Adult-onset idiopathic dystonia is a common movement disorder. Robust evidence advocates in favour of a network disorder with sensory, motor and cerebellar involvement. Seemingly important, many patients may experience comorbid mood disorders or anxiety disorders. Furthermore, these may precede and persist throughout the course of the dystonia, impacting negatively on the quality of life of patients. Vastly understudied, the present study aims to conduct a systematic review of the literature on the prevalence of mood disorders and anxiety in patients with dystonia.

We performed a systematic review in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines searching terms related to dystonia, mood disorders and anxiety. Data was extracted independently by two authors and cross checked to reach a consensus.

A total of 5033 studies were retrieved up to November 2018, 116 met selection criteria; 48 for anxiety disorders, yielding a population of 5075 patients and 68 for depression, providing a total of 10,311 patients. Validated structured interviews reported a prevalence of 37%-45% for anxiety disorders and 24%-39% for any depressive disorder. When applying validated rating scales the prevalence of anxiety disorders ranged from 21%-61%; depressive disorders varied from 20%-52%. The most frequent instruments used to assess anxiety disorders were the Beck Anxiety Inventory, Hamilton Anxiety Rating Scale and the State-Trait Anxiety Inventory; for depression the Beck Depression Inventory, Hamilton Depression Rating Scale and the Montgomery and Asberg Depression Rating Scale. Sex specific prevalence estimates were provided only in 1 study. No further details regarding to the level of training of the assessors was specified.

The overall prevalence of anxiety disorders and depression varied considerably depending upon the instruments utilized. This review emphasizes the importance of developing standardized screening procedures to delineate and identify comorbidities appropriately in patients with dystonia.

## Topic: Other Movement Disorders including Pediatric

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### Hereditary spastic paraplegia misdiagnosed as cerebral palsy: Review of pediatric hereditary spastic paraplegia cases in an Alberta cohort

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**Objectives:** Hereditary spastic paraplegia (HSP) is a rare neurogenetic condition, with over 75 identified genes. Age of onset ranges from childhood to late adulthood, and presentation can vary greatly. Cerebral palsy (CP) is defined as a permanent and non-progressive motor impairment, often thought to be caused by pre- or perinatal brain injury. However, an obvious brain injury may not be identified in some children with CP. As HSP can have many overlapping features with CP, misdiagnosis may occur.

**Methods:** From an Alberta clinical registry of patients with HSP, individuals with onset of spasticity in early childhood were identified. Research based exome sequencing was performed to identify known and novel genetic causes for HSP. Confirmation of abnormal results was done in accredited labs.

**Results:** Of a total of 76 families, 26 families and/or individuals had a pediatric presentation of spasticity. Average age of onset was 4.7 years (ranging from < 1 to age 14 years). 7 of 26 families had received an initial diagnosis of CP; the average age of onset in these cases was 2.16 years old (ranging from 1 to 5 years, except one outlier diagnosed with CP at age 13). Whole exome sequencing of these 7 cases identified pathogenic mutations in 4 cases: *PNPLA6* and *SYNE1* (autosomal recessive), *PLP1* (X-linked) and *SPAST* (de novo autosomal dominant).

**Conclusions:** In a child presenting with spastic diplegia with onset in infancy and a normal MRI, without clear history of prematurity, intrauterine growth restriction (IUGR), intrauterine infection or vascular insult, it is important to consider HSP in the differential diagnosis. Accurate diagnosis of HSP has significant implications for prognosis, management, with genetic counseling and estimation of recurrence risk in future children.

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## **PBMC proteome changes in Freidreich's ataxia: Unravelling downregulated Actin $\alpha$ cardiac muscle 1 in patients**

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**Objectives:** Freidreich's ataxia (FRDA) is an autosomal recessive neurodegenerative disorder characterized by cerebellar atrophy and hypertrophic cardiomyopathy. The primary cause of FRDA is the presence of expanded DNA triplet (GAA) repeats in the first intron of the *fxn* gene on chromosome 9q13 which suppresses the expression of the frataxin protein causing neuronal degeneration. There is still no validated biomarker for the diagnosis and prediction of the disease progression or to assess the response of drug treatments.

**Methods:** We performed a case control proteomic study on Peripheral Blood Mononuclear cells (PBMC) to identify differentially expressed proteins in diseased state. PBMC proteomics of homozygous FRDA patients and age- and gender-matched healthy controls was done using two-dimensional difference in-gel electrophoresis (DIGE).

**Results:** Eleven differentially expressed protein spots were selected (fold change  $\geq 2.0$ ;  $P < 0.05$ ) and identified by LC/MS. The identified proteins have known role in the neuroinflammation (Chloride intracellular channel protein 3, Annexin, T complex protein 1; Interferon inducible protein AIM2); cardiomyopathy (Actin  $\alpha$  cardiac muscle 1, Ca/Calmodulin dependent protein kinase,  $\beta$ -enolase, Myosin regulatory light chain 12A); Neuronal apoptosis (Caspase 8); Compromised glucose metabolism (Pyruvate dehydrogenase E1 subunit  $\beta$ ,  $\beta$ -enolase, Sorbin); and Iron transport (transferring precursor). We have shown that upregulation or downregulation of the concerned proteins correlates with the disease pathogenesis.

**Conclusions:** The study provides some potential blood-based biomarker for diagnosis and prognosis of FRDA however, further investigation with improved sensitivity and specificity is required to validate the identified proteins as biomarkers.

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## Restless leg syndrome and cardiovascular and cerebrovascular diseases in the Canadian longitudinal study on aging

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**Objectives:** Several studies indicate associations between restless leg syndrome (RLS) and atherosclerotic diseases. Causality, however, has not been established. We sought to increase the evidence base through an evaluation of the associations of RLS with cardiovascular/cerebrovascular diseases (CVD) and with carotid intimal thickness (cIMT) in a large population-based sample.

**Methods:** Among the 30,097 Canadian Longitudinal Study on Aging (CLSA) participants, we retained those who had completed the Hopkins RLS diagnostic interview. We defined RLS as compatible symptoms  $\geq 3$  times per week. Using multivariate logistic regression, we examined associations of RLS with CVD history and with cIMT. CVD was defined as self-reported heart disease, peripheral vascular disease (PVD), angina, myocardial infarction, coronary artery bypass graft, angiography, transient ischemic attack (TIA) and stroke. cIMT was measured by ultrasound of the carotid artery at the bifurcation of common carotid artery, and  $>75\%$  percentile was considered as abnormal. Results were adjusted for age, sex, hemoglobin, chronic obstructive pulmonary disease, smoking, physical activity, anxiety, and depression.

**Results:** RLS was present in the 2434 (11.9%) of 20449 participants included in analyses. Those with RLS were slightly older ( $64.07 \pm 10.0$  vs.  $62.5 \pm 10.2$  years) and a higher proportion were women (60.6% vs. 47.6%). They had higher BMI ( $29.28 \pm 6.0$  vs.  $27.65 \pm 5.1$ ), were more smoker (50.3% vs. 44.9%) and had less physical activity  $\geq 1$ /week (49.5% vs. 57.8%). Mean difference in cIMT between those with vs. without RLS ( $0.755 \pm 0.17$  vs.  $0.733 \pm 0.17$ ) was  $0.022$ , 95%CI= $0.015-0.030$ . 27.1% of RLS patients were classified with abnormal cIMT compared to 24% of those without (OR=1.13, 95%CI=1.01-1.28). Those with RLS were more likely to have PVD (10.8% vs. 3.4%, OR=2.95, 95%CI=2.48-3.52), angina (6.9% vs. 3.4%, OR=1.81, 95%CI=1.46-2.23) and prior angiography (13.1% vs. 8.1%, OR=1.64, 95%CI=1.41-1.91). TIA and stroke did not differ between groups (4.4% vs. 2.7%, OR=1.29, 95%CI=1.00-1.66 and 2.2% vs. 1.4%, OR=1.31, 95%CI=0.93-1.84, respectively).

**Conclusions:** RLS patients have higher risk of subjective and objective measures of atherosclerosis.



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## **Movement disorders in post stroke patients: A retrospective analysis**

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**Objectives:** To review the prevalence of various movement disorders in post stroke patients at a tertiary, academic center and to characterize the therapeutic response to various treatments in those patients.

**Background:** Movement disorders have been reported in patients post stroke [ref], however there is limited information regarding the prevalence of various post-stroke movement disorders and their response to potential treatments.

**Design and Methods:** We retrospectively reviewed the charts of patients seen in both the stroke and movement disorder clinics at our center. 147 cases were reviewed, and 30 were found to have a movement disorder that developed after stroke. Patients with no other movement disorder than spasticity were excluded. We reviewed the type of movement disorder, mean latency between time of stroke and movement disorder onset, as well as the response to treatment in various movement disorders.

**Results:** Parkinsonism was noted in 18/30(60%), tremor in 7(23.3%), ataxia in 2(6.7%), and myoclonus, dystonia, and restless leg syndrome (RLS) were each noted in 1 patient (3.3% each). Mean latency from stroke to movement disorder onset was 0.61 years. 24/30(80%) patients had a movement disorder targeted symptomatic treatment.

The overall response to medication in patient with parkinsonism was 87.5% (14/16 tried on pharmacotherapy): 9 of 11 (82%) improved on carbidopa-levodopa, 2/2 improved on dopamine agonist and 3/3 improved on a combination of carbidopa-levodopa and dopamine agonists. Each respective tremor patient tried on primidone, topiramate, or implanted with DBS showed improvement.

One tremor patient also improved with baclofen pump implanted for spasticity. The dystonia patient responded to botulinum toxin injection, and the RLS patient responded to dopamine agonists.

**Conclusions:** Mean latency from stroke to movement disorder onset was 0.61 years. Symptomatic treatment improved the movement disorder in the majority of patients, but was only offered to 80%, emphasizing the importance of therapeutic trials in these patents.

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## Utility of eye movement abnormalities in differentiating neurodegenerative versus non-neurodegenerative Parkinsonism

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**Objectives:** To evaluate eye movement abnormalities in patients with neurodegenerative versus non-neurodegenerative parkinsonism.

**Methods:** This is a prospective, single-center, rater-blinded, case control study. Patients with neurodegenerative parkinsonism having at least grade 2 dopaminergic loss on Dopamine Transporter (DaT) scan and patients with non-neurodegenerative parkinsonism confirmed clinically by a movement disorder specialist and by a normal DaT scan were recruited at Cleveland Clinic. Eye movement examination was recorded and shown to two blinded movement disorder specialists to assess pursuit, saccades, presence of gaze limitation, nystagmus and square-wave jerks. Rater-agreed observations were included in further analysis. Sensitivity, specificity, positive predictive value, negative predictive value, and total accuracy were calculated for the presence of each eye movement abnormality against the DaT scan as the gold standard diagnostic tool.

**Results:** 99 subjects were included in the study, 50 of whom had abnormal DaT scan. Among subjects where there was inter-rater agreement, the prevalence of pursuit abnormalities and saccadic abnormalities was 43.7% and 46.4%, respectively. The inter-rater agreement was found to be moderate for pursuit abnormalities ( $\kappa=0.45$ ), and slight to moderate for saccadic abnormalities ( $\kappa=0.40$ ). For pursuit abnormalities, sensitivity for detecting neurodegenerative parkinsonism was 47.1% and specificity was 59.5%. For saccadic abnormalities, sensitivity was 51.4% and specificity was 58.8%. Nystagmus, square wave jerks, and gaze limitation all had relatively low prevalence in our study population.

**Conclusions:** Abnormalities in pursuit and saccades are likely not useful in distinguishing neurodegenerative versus non-neurodegenerative parkinsonism. The prevalence of nystagmus, square wave jerks, and gaze limitation was too low in our study population to draw any conclusions regarding these clinical signs.

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## Pilot study of cardio-vascular-metabolic risk factors intercepting with neuro-cognition in Atypical Parkinsonism syndrome (aPS) and tardive dyskinesia in schizophrenia

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**Background:** The mechanisms of cardio-vascular-metabolic risks interacting with Atypical Parkinsonism syndrome (aPS) and tardive dyskinesia (TD) in chronic schizophrenics treated with first-generation or second-generation antipsychotics (FGA; SGA) remain uncertain.

**Objectives:** We conducted a post-hoc analysis of aPS and TD in the RCT augmentation Ginsana-115 trial in schizophrenia. From the data, we examined whether aPS measured with Simpson Angus Scale (SAS) and TD measured with Abnormal Involuntary Movement (AIMS) is correlated with: 1) Framingham risk score (FRS) for Cardio-vascular-metabolic (CVM) risks; 2) Insulin resistance (HOMA model) and dyslipidemia (plasma levels of High-density-lipoprotein HDL; low-density-lipoprotein LDC and triglyceride). Our second objective was to examine whether aPS and TD are related to neurocognition assessed with Neurocognitive Screening (NCS)[ Gur-U. Penn].

**Results:** We recruited 44 SGA-treated schizophrenic subjects: mean age 38 yrs, male/female:29/15) with baseline SAS scores 4.2 (SD=3.9); 52.3% (23/44) SAS score > 3.0 and 34.1% (15/44) SAS score > 6. Pearson correlation coefficients of SAS and AIMS scores were used for neurocognitive measures, IR, lipid profile and FRS scores. Baseline SAS scores correlated significantly and directly with log-IR ( $r=0.44, p=0.008$ ). SAS score correlated inversely with HDL ( $r=-0.57, p<0.0001$ ) and directly with LDL ( $r=0.50, p<0.001$ ) and triglyceride ( $r=0.335, p=0.034$ ). Both SAS and AIMS scores correlated significantly with FRS scores (SAS:  $r=0.60, p<0.001$ ; AIMS  $r=0.36, p<0.0001$ ) and independent of ( $r=0.20$ ) of Body mass index (BMI). Higher SAS scores correlated significantly with impaired neurocognitive index ( $r>0.30, p<.05$ ) and selected cognitive domains ( $r>0.30, p<.05$ ). AIMS scores correlated significantly with memory ( $r=0.32, p=0.037$ ).

**Conclusions:** Our findings that in schizophrenia patients, aPS and TD are related to dysregulated insulin resistance, lipid signaling and cardio-vascular homeostasis, and underscore the significance of heart-gut-brain nexus in Parkinson's disease (PD) and aPS and TD. Larger longitudinal studies are warranted to explore balanced lifestyle interventions in movement disorders.

## Topic: Movement disorders

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### Characterizing large cohorts with a rare neurodegenerative disease, progressive supranuclear palsy, from medical claims databases

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**Objectives:** Progressive supranuclear palsy (PSP), a rare neurodegenerative disease, has not been characterized in real world settings regarding the prevalence of comorbidities and acute health events pre- and post-diagnosis. This study characterized cohorts with PSP derived from electronic medical claims databases to gain insight into their disease burden.

**Methods:** This cohort study included patients diagnosed with Steele-Richardson-Olszewski Ophthalmologica (ICD-10 G23.1), the most common diagnosis code for identifying PSP, who were aged 40+ years and continuously enrolled for 365 days prior to the first PSP diagnosis and 180 days after. A cohort was constructed from each of two US databases: MarketScan® with combined commercial and Medicare supplemental claims, and Optum Clinformatics™ for the period 2010-2017. A total 1,044 patients were identified. Demographics, select comorbidities, prior neurodegenerative diseases and frequency of acute events were examined.

**Results:** Overall, the male:female ratio was even. At diagnosis, the mean age of those aged 65+ years was in the mid-70s and for those aged < 65, years in the late 50's. Two-thirds had a diagnosis of Parkinson's disease prior to the first PSP diagnosis. In both cohorts, those without a neurodegenerative disease prior to the first diagnosis of PSP were significantly younger ( $p < 0.05$ ) and had a lower proportion of hypertension ( $p < 0.01$ ) than those with a prior neurodegenerative disease. Among those aged 65+ years, hypertension and mood disorders were statistically significantly higher in both cohorts compared to the general population of elderly ( $p < 0.01$ ). Treated falls affected approximately one-third of both cohorts before and after the first PSP diagnosis. There was no significant change in the incidence rate of acute respiratory infections pre- and post- first diagnosis.

**Conclusions:** We defined the scope of comorbidities and acute events in large real world populations of persons with PSP for which management and prevention strategies could be developed.

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## Turkish version quality of life in essential tremor questionnaire (quest): Validity and reliability study

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**Background:** Our aim was to translate the Quality of Life in Essential Tremor Questionnaire (QUEST) advanced by Troster (2005) and to analyse the validity and reliability of this questionnaire.

**Methods:** Two hundred twelve consecutive patients with essential tremor (ET) and forty-three control subjects were included in the study. Permission for the translation and validation of the QUEST scale was obtained. The translation was performed according to the guidelines provided by the publisher. After the translation, the final version of the scale was administered to both groups to determine its reliability and validity.

**Results:** The QUEST Physical, Psychosocial, communication, Hobbies/leisure and Work/finance scores were 0.967, 0.968, 0.933, 0.964 and 0.925, respectively. There were good correlations between each of the QUEST scores that were indicative of good internal consistency. Additionally, we observed that all of the QUEST scores were most strongly related to the right and left arms ( $p=0.0001$ ). However, we observed that all of the QUEST scores were weakly related to the voice, head and right leg ( $p=0.0001$ ).

**Discussion:** These findings support the notion that the Turkish version of the Quality of Life in Essential Tremor (QUEST) questionnaire is a valid and reliable tool for the assessment of the quality of life of patients with ET.

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## Co-prevalence of essential tremor and parkinsonism - an autopsy study

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**Objectives:** To study clinical and pathological characteristics of ET and concurrent PS cases.

**Methods:** Movement Disorders Clinics Saskatchewan (MDCS) has operated uninterrupted since 1968. All essential tremor (ET) patients followed at MDCS with subsequent onset of parkinsonism (PS) onset were included. Patients were evaluated by the same two movement disorder neurologists. Patients seen at MDCS are offered choice of autopsy at no cost. Autopsy is performed within 24 hours of death. One-half brain is studied by a neuropathologist and other half preserved at  $-80^{\circ}\text{C}$ . Final diagnosis is made by the treating neurologist, considering all clinical and pathology information.

**Results:** 590 cases seen at MDCS came to autopsy between 1968 and 2018. Sixty-nine (12%) of those had a diagnosis of ET; 21 (30%) in that group had a second clinical and/or pathology diagnosis of PS. The most common clinicopathological form of PS was Parkinson's disease (PD) alone or with another disorder in 14 (67%), followed by progressive supranuclear palsy (PSP) in 5 (24%). The most reliable findings for onset of PS were emergence of asymmetrical bradykinesia or lower limb resting tremor. Most patients with dual

diagnosis had symptomatic benefit on levodopa. The most common error for PD diagnosis was the PSP cases without gaze palsy. The dual diagnosis clinical picture evolved with time. Four patients changed from an early tremor-dominant to akinetic-rigid profile. We have documented that on videos.

**Conclusions:** All known common variants of PS may co-occur with ET. The relative frequency is similar to that in our autopsy series. Considering significant errors in the clinical diagnosis of each PD and ET, autopsy study represents the most reliable method to determine the cause of parkinsonism in ET cases.

## P 200

### Effects of GABA<sub>A</sub> receptor positive allosteric modulator, SAGE-217, on essential tremor: An open label, phase 2 pilot clinical trial

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Open-label, Ph2 trial evaluated efficacy, safety and PK of the GABA<sub>A</sub> receptor positive allosteric modulator (PAM) SAGE-217 in subjects with essential tremor (ET).

Subjects 18-80yrs, diagnosed with ET >5yrs prior to screening were enrolled to receive SAGE-217 oral capsules (30 mg) for 7 days in the morning. ET was defined as bilateral postural tremor and kinetic tremor, involving hands and forearms, that is visible and persistent. Subjects had bilateral The Essential Tremor Rating Scale (TETRAS) scores of ≥2 on each side for kinetic tremor (Performance subscale item 4c) and a score of ≥2 for either wing beating or forward outstretched postural tremor. The primary efficacy endpoint was reduction in tremor severity by accelerometer-based Kinesia™ kinetic tremor combined (right + left) score on Day 7. Secondary endpoints included tremor severity assessment by Kinesia™ upper limb (UL) tremor score and TETRAS on Day 7. Safety was assessed by monitoring adverse events (AEs).

14 subjects, age 62.4 (±8.34) years, were enrolled with mean time (±SD) since ET diagnosis of 22.6yrs (±16.84). Administration of SAGE-217 for 7 days significantly improved combined kinetic tremor symptoms by 14% (p=0.0016) and total UL tremor symptoms by 19.2% (2.4 point decrease from mean baseline score (10.5) as assessed by accelerometry (Kinesia™). SAGE-217 decreased tremor, as assessed by the change from baseline in TETRAS scores (-36.0% TETRAS kinetic tremor, -34.4% UL Combined score). There were no serious AEs, no patients discontinued treatment. The proportion of subjects reporting TEAEs was 50% (7/14). The most common AEs were somnolence, dizziness, and sedation.

SAGE-217 was generally well-tolerated. The improved tremor symptoms demonstrated by Kinesia™ and TETRAS UL combined kinetic and total scores support the continued development of GABA<sub>A</sub> receptor PAMs in ET.

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## Emotional regulation and its neural substrate in functional neurological disorders

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**Background:** Functional neurological disorders (FND) has been historically conceived as unconscious emotional reactions to stress. FND are common in neurology wards with the levels of disability similar to epilepsy or multiple sclerosis (Stone et al., 2010).

Previous studies reported failure to habituate to negative emotional stimuli in FND and framed functional symptoms as abnormal behavioral-motor responses. However, a capacity to voluntarily control negative emotional reactions in FND is mostly unknown. Therefore, we aimed to examine differences in emotional regulation strategies and underlying brain processes among FND patients, patients with psychogenic epileptic seizures and healthy controls.

**Methods:** An event-related functional magnetic resonance imaging (fMRI) emotion regulation task was completed by 16 functional movement disorder, 15 psychogenic nonepileptic seizure patients and 29 age and sex-matched healthy controls. In the observation condition, the subjects watched neutral or negative pictures from International Affective Picture System. In the regulation condition, the participants tried to down-regulate emotional responses to negative pictures. The emotional regulation strategy was assessed after the completion of the task. The fMRI session was performed at 3 Tesla Siemens Prisma.

**Results:** The patient groups did not differ in reported emotion regulation strategy but we found increased activation in brain areas implicated in motor inhibition in functional movement disorder patients compared to psychogenic nonepileptic seizure patients during emotional regulation.

**Conclusions:** Functional movement disorder and psychogenic nonepileptic seizure patients show distinct brain activation during emotional regulation with functional movement disorder engaging more cognitive control processes in response to emotional stimuli.

**References:** Stone J, Warlow C, Sharpe M. The symptom of functional weakness: a controlled study of 107 patients. *Brain* 2010; 133(Pt 5):1537-51.

**Funding:** This study is supported by Ministry of Health of the Czech Republic, grant no. 16-31457A. All rights reserved.

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## Confirmed safety of deutetrabenazine for tardive dyskinesia in a 3-year open-label extension study

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**Objectives:** Deutetrabenazine (Austedo) is approved by the FDA for treatment of tardive dyskinesia (TD) in adults. In the 12-week ARM-TD and AIM-TD studies, deutetrabenazine showed clinically significant improvements in Abnormal Involuntary Movement Scale scores compared with placebo, and there were low rates of overall adverse events (AEs) and discontinuations associated with deutetrabenazine. The objective of this study was to evaluate the long-term safety and tolerability of deutetrabenazine in patients with TD at 3 years.

**Methods:** Patients who completed ARM-TD or AIM-TD were included in this open-label (OL), single-arm extension study, in which all patients restarted/started deutetrabenazine 12 mg/day, titrating up to a maximum total daily dose of 48 mg/day based on dyskinesia control and tolerability. The study comprised a 6-week titration period and a long-term maintenance phase. Safety measures included incidence of AEs, serious AEs (SAEs), and AEs leading to withdrawal, dose reduction, or dose suspension. Exposure-adjusted incidence rates (EAIRs; incidence/patient-years) were used for calculating AE frequencies. This analysis reports results up to Week 158.

**Results:** 343 patients were enrolled (111 received placebo, 232 received deutetrabenazine in the parent studies; 183 patients currently receiving treatment, 259 completed 1 year, 172 completed 2 years, 41 completed 3 years). There were 623 patient-years of exposure, and the maximum dose was reached by >40% of patients. Exposure-adjusted incidence rates (EAIRs) of AEs were comparable to or lower than those observed with short-term deutetrabenazine and placebo. The frequency of SAEs (EAIR 0.10) was similar to that observed with short-term placebo (0.33) and short-term deutetrabenazine (range 0.06-0.33) treatment. AEs leading to withdrawal (0.06), dose reduction (0.10), and dose suspension (0.05) were uncommon.

**Conclusions:** These results confirm the safety outcomes observed in the ARM-TD and AIM-TD parent studies, demonstrating that deutetrabenazine is well tolerated for long-term use in TD patients.



## Long-term safety and tolerability of once-daily Valbenazine in patients with tardive dyskinesia

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**Objectives:** To evaluate long-term safety and tolerability of once-daily valbenazine in adults with tardive dyskinesia (TD).

**Methods:** Data were pooled from KINECT 3 (NCT02274558: 6-week double-blind placebo-controlled period, followed by a 42-week double-blind extension and 4-week drug-free washout) and KINECT 4 (NCT02405091: 48-week open-label treatment period and 4-week drug-free washout). KINECT 3/4 completers were eligible to enroll in a subsequent rollover study (NCT02736955: 72 weeks of open-label treatment or until valbenazine became commercially available); data from the rollover study were described separately. Safety assessments included treatment-emergent adverse events (TEAEs), vital signs, and electrocardiogram. Psychiatric status was assessed in KINECT 3/4 using Positive and Negative Syndrome Scale (PANSS) and Calgary Depression Scale for Schizophrenia (CDSS) for schizophrenia/schizoaffective disorder participants; Montgomery-Åsberg Depression Rating Scale (MADRS) and Young Mania Rating Scale (YMRS) for mood disorder participants.

**Results:** Analyses included 304 KINECT 3/4 participants and 160 rollover participants. In KINECT 3/4, 71.7% of participants reported any TEAE, 16.8% a serious TEAE, and 15.5% discontinued due to a TEAE. TEAEs reported in ≥5% of all KINECT 3/4 participants were headache (8.9%), urinary tract infection (8.9%), somnolence (7.9%), fatigue (6.3%), dizziness (5.9%), and suicidal ideation (5.6%). In the rollover, 53.1% of participants reported any TEAE, 10.0% a serious TEAE, and 5.6% discontinued due to a TEAE. The most common rollover TEAEs were back pain and urinary tract infection (each, 4.4%). There were no clinically important changes in vital signs or electrocardiograms. Psychiatric status generally remained stable in KINECT 3/4, as indicated by mean changes from baseline to Week 48 (PANSS total, -3.2; CDSS, -0.5; MADRS, 0.3; YMRS, -1.0).

**Conclusions:** Valbenazine was well tolerated in adults who received >1 year of treatment; no new safety signals observed. Psychiatric stability was generally maintained in schizophrenia/schizoaffective and mood disorder participants. Once-daily valbenazine may be an appropriate treatment for the long-term management of TD.

## P 204

**Measuring ATXN3 Levels in SCA3 patients**

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**Background:** Spinocerebellar ataxia 3 (SCA3) is characterized by the accumulation of polyglutamine (polyQ) protein aggregates derived from translation of the CAG trinucleotide expansions in ataxin 3 (ATXN3). As the rising length of nucleotide repeats correlate with disease severity, reducing mutant ATXN3 may ameliorate the symptoms. A biomarker is necessary to monitor disease progression and aid in the therapeutic intervention. In efforts to develop a reliable biomarker, mutant ATXN3 levels were measured in plasma, and cerebrospinal fluid (CSF).

**Methods:** Plasma and CSF samples were collected from 28 unaffected and affected SCA3 patients in different stages of their illness from mild to severe and 18 controls. We developed sandwich ELISAs to detect mutant ATXN3. Electrochemiluminescent immunoassays employing the Meso Scale Discovery (MSD) system were utilized.

**Results:** PolyQ ATXN3 proteins were detected not only in CSF but in plasma of SCA3 individuals; they were compared to healthy controls. PolyQ ATXN3 proteins significantly accumulated in SCA3 patients.

**Conclusions:** While no validated biomarker of this kind yet exists, polyQ ATXN3 proteins may be most suitable to fill this urgent need. Confirmation that polyQ ATXN3 proteins are measureable in CSF and peripheral blood would greatly facilitate identification and diagnosing SCA3 patients and asymptomatic carriers. While further studies are warranted, the preliminary data presented is clearly a promising first step in establishing whether mutant ATXN3 proteins may be useful clinical biomarkers for SCA3.

## P 206

**The effects of valbenazine on abnormal involuntary movement scale items 8, 9, and 10: Results from the KINECT 4 Study**

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**Objectives:** KINECT 4 (NCT02405091), a long-term study of once-daily valbenazine, demonstrated sustained reductions in tardive dyskinesia (TD) severity based on the Abnormal Involuntary Movement Scale (AIMS) total score (sum of items 1-7). AIMS items 8 (overall severity), 9 (incapacitation), and 10 (patient's awareness/distress) were examined to provide additional context for valbenazine effects in patients with TD.

**Methods:** KINECT 4 included 48 weeks of treatment followed by 4 weeks of washout. Key eligibility criteria included: ages 18-85 years; DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or mood disorder; neuroleptic-induced TD for  $\geq 3$  months. Most participants (88.3%) were taking antipsychotic medication at baseline. Valbenazine was initiated at 40mg; at Week 4, dosage escalation to 80mg was allowed (reduction to 40mg was allowed based on tolerability, 80/40mg group). For items 8-10, mean changes from baseline to Weeks 48 and 52 were described. A shift analysis was conducted for items 8 and 9.

**Results:** At Week 48 (end of treatment: 40mg, n=20; 80mg, n=74; 80/40mg, n=9), mean improvements from baseline were -1.9, -2.1, and -1.2 for item 8; -1.9, -2.0, and -1.0 for item 9; and -1.9, -2.0, and -0.9 for item 10, with 40mg, 80mg, and 80/40mg, respectively. At Week 52 (end of 4-week washout), mean changes were smaller but indicated continued improvement from baseline (range: -0.7 to -1.3). Among participants who had item 8 or 9 baseline scores  $\geq 3$  (moderate/severe), most shifted to  $\leq 2$  (none/mild) at Week 48: item 8 (40mg, 94.4% [17/18]; 80mg, 97.3% [71/73]; 80/40mg, 85.7% [6/7]); item 9 (40mg, 100% [10/10]; 80mg, 97.8% [45/46]; 80/40mg, 100% [3/3]). At Week 52, >40% maintained this clinically meaningful improvement after washout.

**Conclusions:** Long-term treatment with once-daily valbenazine (40 or 80mg) improved overall severity of abnormal movements, incapacitation due to abnormal movements, and patient awareness/distress.

## P 207

### Efficacy and safety of deutetrabenazine in patients with mild tardive dyskinesia: Analysis of the ARM-TD and AIM-TD Studies

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**Objectives:** Tardive dyskinesia (TD) is an involuntary, often-irreversible movement disorder that can affect any body region. Deutetrabenazine treatment was approved by the US Food and Drug Administration for treatment of TD on the basis of two pivotal studies, in which statistically and clinically significant reductions in Abnormal Involuntary Movement Scale (AIMS) scores at Week 12 versus placebo (primary endpoint) were demonstrated in patients with baseline AIMS scores  $\geq 6$ .

The objective of this study was to evaluate the efficacy and safety of deutetrabenazine, as measured by change in AIMS scores, in patients with mild TD (AIMS score < 6) from the pooled ARM-TD and AIM-TD studies.

**Methods:** ARM-TD and AIM-TD were 12-week, randomized, double-blind, placebo-controlled studies evaluating the safety and efficacy of deutetrabenazine in the treatment of TD. Here we report the change in AIMS score from baseline to Week 12 for patients with mild TD. Patients from the deutetrabenazine arm of ARM-TD (end of treatment mean dose 38.3 mg/day) and the 24 and 36 mg/day arms of AIM-TD were pooled and compared with the pooled placebo group.

**Results:** A total of 58 patients (n=20, placebo; n=38, deutetrabenazine) with AIMS scores < 6 at baseline were included in the analysis. The mean ( $\pm$  standard deviation) change in AIMS score from baseline to Week 12 was -0.89 ( $\pm$ 1.91) versus 0.2 ( $\pm$ 1.67) in the deutetrabenazine and placebo groups, respectively (least-squares mean difference: -0.92; P=0.08). At Week 12, patients receiving deutetrabenazine showed a change in AIMS scores of -15.7%, versus 7.0% for those receiving placebo. A total of 39.5% of patients receiving deutetrabenazine achieved a  $\geq$ 50% reduction in AIMS scores compared with 5.0% of patients receiving placebo (P=0.005).

**Conclusions:** Patients with AIMS scores < 6 at baseline showed score improvements at Week 12, suggesting clinical benefit for deutetrabenazine in the treatment of mild TD.

## P 208

### Measuring tremor continuously and in real-world contexts using a wearable device during an essential tremor clinical trial

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Essential tremor (ET) is a common movement disorder characterized by tremor, commonly in the hand, during voluntary movements or maintenance of a posture. The standard for measuring tremor severity in clinical trials is clinical assessments, which is limited by clinic visits and infrequent sampling. Wearable devices could provide significant value by measuring tremor continuously. We present data from an open-label Phase 2a trial evaluating the effects of SAGE-217, an investigational GABA-A positive allosteric modulator, in patients with ET. The objective is to compare tremor measurements from a wearable wristband device (E4 wristband, Empatica, Milano) against clinical scales, and determine whether the device can detect pharmacological modulation of tremor.

At regular time intervals prior to and following SAGE-217 administration, subjects were assessed in the clinic with the TETRAS clinical scale and a finger-worn accelerometer (Kinesia ONE, Great Lakes NeuroTechnologies, Cleveland) worn during defined tasks. The wristband device was continuously worn by patients during the trial and measurements were captured both inside and outside of the clinic.

In most subjects, an oscillating signal within the expected tremor-frequency range (3-8 Hz) was clearly measurable from the wristband device. Custom algorithms were developed to derive a continuous, time-varying tremor score from the device. Across subjects, the mean wristband-derived tremor score over the trial correlated with both TETRAS score ( $r=0.68$ ,  $p<0.01$ ) and Kinesia score ( $r=0.86$ ,  $p<0.0001$ ).

Administration of SAGE-217 resulted in a reduction of tremor that was measurable based on the TETRAS, Kinesia, and the Empatica wristband device. Additionally, effects of SAGE-217 and their time course were also measurable from patients wearing the device outside of the clinic. These results suggest a wearable device may be able to accurately and continuously measure tremor in clinical trial settings and could provide additional value by measuring tremor in real-world situations outside of clinical assessment windows.

P 209

## **ABBV-8E12, a humanized anti-tau monoclonal antibody for treatment of progressive supranuclear palsy and early Alzheimer's disease: Design and updated baseline characteristics of phase 2 studies**

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**Objectives:** ABBV-8E12 is a humanized anti-tau monoclonal antibody being developed for treatment of Progressive Supranuclear Palsy (PSP) and Early Alzheimer's Disease (AD). Here we present the designs and latest baseline characteristics of phase 2 studies in PSP and Early AD patients.

**Methods:** One phase 2, double-blind, placebo-controlled study assesses the 52-week efficacy and safety of ABBV-8E12 in PSP subjects (NCT02985879) and is now fully enrolled with 378 patients. A second phase 2, double-blind, placebo-controlled study assesses the 96-week efficacy and safety of ABBV-8E12 in Early AD patients (NCT02880956). A total of 400 patients (55-85 years) will be enrolled at approximately 65 global study sites; 316 patients were enrolled as of January 11, 2019.

**Results:** For the PSP study, baseline characteristics for the first 370 patients enrolled include: age (median [range]=69 [49-86] years); gender (% male=58.6%); Body Mass Index (BMI) (median [range]=26.4 [17.6-42.6] kg/m<sup>2</sup>); Mini-Mental State Examination (MMSE) score (mean±SD=26.0±3.3); and PSP Rating Scale (PSPRS) total score (mean±SD=36.3±11.6).

The primary efficacy outcome in this study is the change in PSPRS total score from baseline to Week 52. For the Early AD study, baseline characteristics include: age, (median[range] =72[55-86] years; MMSE score (mean±SD=24.5±2.9); and Clinical Dementia Rating-Sum of Boxes (CDR-SB) (mean±SD=3.03±1.16). Primary efficacy outcome in this study is the change in CDR-SB from baseline to Week 96.

**Conclusions:** A significant unmet medical need exists for the development of disease-modifying drugs for PSP and AD which directly impact the biology of the diseases and reduce associated burdens. The current studies are designed to evaluate the efficacy and safety of ABBV-8E12 in PSP and Early AD patients.

P 210

## **Treatment of RLS augmentation with the D1 specific antagonist ecopipam, an exploratory placebo controlled cross-over trial**

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**Objectives:** Dopamine agonists (DA) initially dramatically improve restless legs syndrome (RLS), however long-term treatment often results in augmentation, where the baseline RLS intensity markedly worsens. There is no established strategy aside from DA discontinuation, which is extremely difficult. Based on animal studies, upregulation of dopamine type 1 receptors in the spinal cord may account for augmentation.

We tested the safety and explored efficacy of ecopipam, the only D1 specific antagonist (DA), in a population of RLS patients with dopamine agonist induced augmentation.

**Methods:** This is an exploratory placebo controlled 6 week/arm cross-over trial of ecopipam (25mg-100mg). Patients continued their DA. Tolerability was primary. Efficacy assessments included the IRLS, RLS diaries, and clinical global impressions.

**Results:** 9/10 subjects completed the trial, 1 dropped for logistical reasons after the first leg, which was active drug. Tolerability was very good. The most common adverse event was sedation (5 drug vs 3 placebo). There was no rebound exacerbation after ecopipam discontinuation. Efficacy results were complicated by a carry-over effect and placebo response. CGI favored active drug 3.3 vs 3.94, but did not correlate with IRLS scores, which were not significantly different, and showed very high variance. Three- day RLS diary data favored active drug (10.2 hours vs. 15.0 hours),  $p=0.2$ .

**Conclusions:** Ecopipam was safe and demonstrated encouraging results in augmented RLS patients.

## P 211

### The prevalence of essential tremor in edirne and its districts concomitant comorbid conditions

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We aimed to determine the prevalence and risk factors of Essential Tremor (ET) in Edirne and its districts, located in Western Thrace, which is the most western part of Turkey. In this study, 3008 individuals who could communicate and agreed to participate in the study were evaluated. To obtain the data from the applicants in 30 Family Health Centres in Edirne and its districts, a face-to-face questionnaire that consisted of 43 questions was prepared by the researchers. The questionnaire included general information, questions to evaluate potential concomitant comorbid conditions and questions regarding the symptomatology used in ET diagnosis, as well as questions to evaluate ET severity was examined with spiral test. Patients were classified by using Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET) diagnostic and clinical evaluation scale. According to the diagnostic criteria for ET (used in participants who were examined and in those whose medical records were reviewed) were similar to those used in a study conducted in Turkey. Of 3008 individuals, 173 were diagnosed with ET according to the questionnaire results from Edirne and its districts, and the prevalence of ET was 5.8%. Approximately, 43.4% of the patients with ET were male, and 56.6% were female, which was not significantly different ( $p > 0.05$ ). Participants with tremor related to alcohol withdrawal, hyperthyroidism, anxiety, depression other known causes of tremor were not considered to have ET.

ET prevalence studies will increase the awareness of the community and provide early diagnosis and treatment, as well as serve as a basis to reduce morbidity and improve the quality of life.

P 212

## Reliability and efficiency of using handheld telehealth technology to screen for spasticity

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**Objectives:** Spasticity is underdiagnosed and often leads to significant problems when left untreated. To test the reliability and efficiency of telehealth as a screening tool for spasticity, movement disorders neurologists at Vanderbilt University Medical Center (VUMC) used hand-held technology facilitated by a bedside nurse to remotely screen for the signs or symptoms of spasticity in residents with intellectual disabilities residing in a long-term care facility.

**Methods:** In-person examinations of residents (n=17) with intellectual disabilities residing in long-term care facilities were performed by a VUMC movement disorders neurologist to determine the presence of spasticity. Subsequent to the in-person exam, two different VUMC movement disorders neurologists independently connected via telehealth technology to a bedside nurse facilitating an abbreviated screening examination for signs or symptoms suggesting the possible presence of spasticity. To measure efficiency, each teleneurology examination was timed by a research coordinator.

**Results:** The time to complete a telehealth spasticity screening examination was 3 minutes ( $\pm$  61 seconds). The two telehealth neurology examiners had a sensitivity of 73% and 82%, a negative predictive value (NPV) of 63% and 71%, and a specificity and positive predictive value (PPV) of 100% in the identification of spasticity.

There was almost perfect agreement between the two telehealth neurologists (Kappa = 0.88, 95%CI 0.64-1.00). One participant withdrew consent and was not included in these analyses.

**Conclusions:** Handheld telehealth technology is a quick way to perform spasticity screening examinations and resulted in high sensitivity and NPV, as well as perfect specificity and PPV. These findings suggest that telehealth technology is likely a reliable and efficient screening tool for use in identifying individuals who may benefit from evaluation and treatment of spasticity. To validate our findings, additional research should be done with a larger cohort.

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## The exercise interventions effects on movement disorder in patients with Parkinson's disease

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**Background:** Parkinson's disease is a CNS disease of senile characterized with gradual and progressive muscular rigidity, tremor and the loss of locomotor skills. The aim of the present study was to review the exercise/physical interventions relevant to the treatment of idiopathic Parkinson's disease.

**Materials and Methods:** This review was done using a systematic search in Sportdi, PubMed, Medline, and Google Scholar cites on papers published during 2005-2017 in the field of training, exercise/movement therapy on Parkinson. Moreover, the review was done in four categories: postural instability, balance performance, quality of life, walking and risk of falling.

**Results:** Despite the diversity in training program, the majority of studies reported significant benefits in addition to the conventional medical treatments on the movement performance in Parkinson's disease.

**Conclusions:** Given the effectiveness of exercise in the improvement of different aspects of movement performance among the Parkinson patients, in future the clinicians are required to take special consideration on applying movement therapy along with medical treatments for specific measurements on the biomechanical aspects of the disease.

**Keywords:** Parkinson, Movement therapy, Walking, Balance, Quality of life

## P 214

### Improving functional tremor using mirror box therapy

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**Objectives:** To investigate the potential of using a mirror box as a therapeutic intervention amongst patients with functional movement disorder (FMD). There are currently no known effective and sustainable treatments for FMD. Previous studies have shown beneficial effects of mirror therapy for the treatment of stroke and phantom limb pain. No study to date has been done to evaluate the efficacy of mirror therapy in FMD.

**Methods:** We conducted a prospective, open-label, rater-blinded, single center, pilot clinical trial. Patients diagnosed with FMD by a movement disorder specialist presenting with unilateral or asymmetrical bilateral involuntary movement of upper extremity(s) were recruited. Exclusion criteria included severe symmetrical upper extremity involuntary movements, cognitive impairment, movements that could interfere with the apparatus, limb hemiparesis, or loss of one arm. Patients were asked to perform five 30-second hand exercises with the less affected hand followed by both hands simultaneously, in the presence and absence of a mirror box. The mirror box enabled patients to see the reflection of the less affected hand during hand exercises while obscuring the more affected hand. The order of mirror box versus no mirror box was randomized across patients. Tremors were recorded and rated by blinded movement disorder specialists using the simplified Functional Movement Disorder Rating Scale(s-FMDRS). The primary outcome was the change in s-FMDRS score in the more affected hand following the intervention.

**Results:** Results to be presented pending statistical analyses.



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## Clinical manifestations of psycho pathology conditions of as non motor symptoms of multiply sclerosis

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MS is an inflammatory and autoimmune disease of CNS, wich selectively affects myelin layer of nerve fiber, mainly affects young people. The course and prognosis of MS significantly worsens with addition of depressive disorders, occurring in 40-70% of cases with MS.

**Purpose:** Of the research is to study depression at MS, differentiated approach to therapy.

We used clinical-psychopathological, psychometry methods (scales of depression and anxiety). We observed 29 (100%) patients with definite diagnosis of MS according to the criteria of Ch. Poser. Duration of the disease more than two years, with average age of  $33.2 \pm 8.7$  years old.

At 41.4% of patients the disease began with pyramidal symptoms in the form of paresis, and in 27.6% of them - disorders of the coordinating sphere. Symptoms of dysesthesia were observed in 10.3% of the patients, lesions of visual analyzer observed in 14%. 21 (72%) people had remitting, 8 (27.6%) - progressive type of multiple sclerosis. 18 (58.6%) patients received immunomodulatory, 21 (72.4%) symptomatic therapy. 6.9 % of patients with MS had masked depression, 20.7% mild depression, 72.4% had a tendency to depression. With coordinated and pelvic dysfunctions, tendency to depression increased, which manifested itself in the form of irritability and feeling of frustration. Depression was found in the early stages of MS, when there were no deep motor dysfunctions. High level of anxiety was observed in 17.2% and average level in 41.4% of the patients, the highest percentage of high level of anxiety was observed in patients with cerebellar insufficiency and vestibular disorders.

Thus, anxiety and depression are often found in patients with MS who need treatment that affects medical-physical, socio-psychological quality of life.

P 218

## Clinical course of facial palsy in patients with multiple sclerosis

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MS remains relevant due to increase in the incidence rate, lesion of young, mobility patients, high disability, significant economic costs. One of the pathognomonic symptoms of MS is paresis of the facial nerve.

**Purpose:** was to study motor activity of mimic muscles in patients with MS.

23 patients were surveyed. 9 (39.1%) patients were with peripheral paresis of facial nerve in MS (1<sup>st</sup> group) and 14 (60.8%) patients with facial palsy without of MS (2<sup>nd</sup> group). There were performed clinical and MND facial muscles electroneurogram for 10 months.

There were noted asymmetry and hypomimia of the face, followed by difficulties in speech, food intake, logophthalmus on the side of prosoparesis. We attracted that patients of the 1<sup>st</sup> group had no loss of taste and pain behind the ear, often developed facial myokymia - constant twitching of the facial muscles,

which, apparently, were associated with the defeat of cortical pathways. We noted that in this group the paresis of the facial nerve had remitting course, There were exacerbation episodes of the facial nerve paresis within 10 months in 22.2% patients; in contrast to the 2<sup>nd</sup> group, where the remitting course was not typical. On ENMG, was detected that patients of the 1<sup>st</sup> group have axonopathy according to the type of reduction in the rate of propagation of arousal (SRV) by 25% of the age norm, and the amplitude of the M-response decreased by 60%, while in the 2<sup>nd</sup> group the SRV was 35% lower than the normative data of age, and the amplitude of the M-response decreased by 65%, which were found as unreliable indicators between the groups ( $t = 0.9$ ).

Thus, the paresis of facial muscles in MS has a relapsing course, with acute stages, and the functional state of the muscles according to ENMG does not differ with NFN without combination of MS.

## P 219

### Onset and progression of pathologic atrophy in patients with Huntington disease in Central Asian regions

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**Objectives:** We aimed to study how caudate and global volumes change as HD progresses from premanifest to early disease.

**Patients and methods:** 32 HD gene-positive individuals and 14 controls underwent serial volumetric MR imaging (baseline, 12 and 24 months; 2 or 3 scans per person). At baseline, 2 patients with HD were pre-manifest but developed overt motor features during the study, and 30 had early HD. All had dates of motor onset recorded. Caudates, lateral ventricles, and TIVs were measured using semiautomated procedures. Linear mixed models were used to investigate differences between HD and controls in relation to motor onset, controlling for TIV, sex, and age.

**Results:** Extrapolating backwards in time, we found that differences in caudate and ventricular volumes between patients with HD and controls were evident 14 and 5 years, respectively, before motor onset ( $P < .05$ ). At onset, caudate volume was 2.56 mL smaller than that in controls ( $P < .0001$ ); ventricular volume was 9.23 mL larger ( $P < .0001$ ). HD caudate atrophy rates were linear, showed low variability between subjects, and were approximately 10-fold higher than those in controls ( $P < .001$ ). HD ventricular enlargement rates were variable between subjects, were approximately 4-fold higher than those in controls at onset ( $P < .001$ ), and accelerated with disease duration ( $P = .02$ ).

**Conclusions:** We provide evidence of acceleration of global atrophy in HD with disproportionate caudate involvement. Both caudate and global measures may be of use as early markers of HD pathology.

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## Adults with Huntington's disease on assisted dying in Uzbekistan: A qualitative exploration

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**Background:** Assisted dying is frequently debated publicly and research often includes the views of health professionals on this issue. However, the views of people with life-limiting conditions, for whom this issue is likely to have a different resonance, are less well represented.

**Aim:** The purpose of this study was to explore the views of people who live with the inevitability of developing Huntington's disease, a genetically transmitted disease which significantly limits life, on assisted dying.

**Methods:** Using thematic analysis methodology, individual semi-structured interviews were conducted. Seven participants (five women and two men) who were gene positive for Huntington's disease took part in the study.

**Results:** Four themes were extracted: (1) autonomy and kindness in assisted dying: the importance of moral principles; (2) Huntington's disease threatens life and emphasises issues relating to death; (3) dilemmas in decision-making on assisted dying: "There are no winners" and (4) the absence of explicit discussion on dying and Huntington's disease: "Elephants in the room".

**Conclusions:** Our findings suggest that talking to patients about assisted death may not cause harm and may even be invited by many patients with Huntington's disease. The perspectives of those who live with Huntington's disease, especially given its extended effects within families, add significant clinical and theoretical insights.

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## Intranasal delivery of insulin for the restoration of memory signaling in Alzheimer disease

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Alzheimer's disease (AD), a form of dementia, is progressive, degenerative brain disease characterized by marked atrophy of cerebral cortex and loss of cortical and sub-cortical neurons. Weakening of insulin receptor signaling is involved in ageing-related brain degeneration such as AD. Objective of this study is to develop delivery-system to overcome BBB by employing novel, non-invasive approach via nasal route. The olfactory neural pathway provides both intraneuronal and extraneuronal pathway into brain. In present study delivery of antibody appended Insulin encapsulated carrier, PEGylated nanoparticle coated with chitosan to facilitate nasal absorption for efficient transfer to brain.

PEGylated-PLGA nanoparticles were prepared by modified Double Emulsification method and coated with chitosan by freeze drying. Characterization was done by FTIR, NMR and *in-vitro* for shape, size, and

drug-entrapment. *In-vivo* study comprised biodistribution in various organs and fluorescence microscopy, estimation of Anti-A $\beta$  antibody, PET-Imaging of Brain, Hemolytic Toxicity studies, Histopathology of Nasal Mucosa and Brain with periodic Blood Glucose Level Monitoring.

Nanoparticles were spherical in shape and smooth. Degree of hemolysis showed PEGylated(PEG-NP's) and chitosan coated nanoparticles(cPEG-NP's) were less toxic. Blood glucose monitoring indicates reduction in blood glucose level in cPEG-NP's. Biodistribution assessment suggests nanoparticles showed maximum availability at olfactory bulb entrance. Chitosan coating increased CSF availability of drug even at initial period of administration. Uptake study shows intense fluorescence in brain revealing higher uptake of nanoparticles. These studies highlight possible biological significance of cPEG-NP's for delivery to brain.

Results from various studies suggest nanoparticles are effective delivery system for targeted delivery of insulin in brain for an extended period. Chitosan coating elicits associated benefits in addition to prolonging uptake via intranasal route. This project may provide sound platform towards employment of this modified nanoparticulate carrier for brain delivery of proteins and peptides towards intranasal delivery of insulin for restoration of memory signaling in Alzheimer patients.

## P 227

### Absence of neurogenic orthostatic hypotension in progressive supranuclear palsy: Is the same true of other tauopathies?

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**Objectives:** To evaluate the pattern and severity of autonomic dysfunction in autopsy-confirmed progressive supranuclear palsy (PSP) in comparison to patients with  $\alpha$ -synuclein pathology.

**Methods:** Autopsy-confirmed cases of 14 PSP, 18 multiple system atrophy (MSA), and 24 Lewy body disease (LBD) patients with antemortem autonomic testing were reviewed retrospectively. All patients underwent comprehensive clinical evaluations by a movement disorder specialist, formal autonomic testing, and postmortem examinations at Mayo Clinic.

**Results:** The absence of orthostatic hypotension (OH) was the strongest autonomic parameter that distinguished PSP from  $\alpha$ -synucleinopathies (0% vs. 69%,  $P < 0.0001$ ). Tests of adrenergic failure, which distinguish neurogenic orthostatic hypotension (nOH), also differentiated PSP from other groups. These included the pressure recovery time ( $P = 0.0008$ ), the adrenergic impairment score ( $P = 0.001$ ), and the magnitude of change of systolic ( $P = 0.0002$ ) and diastolic ( $P = 0.0001$ ) BP during upright tilt. Additionally, REM sleep behavior disorder was seen less frequently ( $P = 0.006$ ) in PSP (33%) in comparison to MSA (87%) and LBD (90%). Antemortem clinical diagnostic accuracy for these phenotypically variable disorders was 57% for PSP and 83% for  $\alpha$ -synucleinopathies.

**Conclusions:** Our results suggest that the cardiovascular adrenergic system, which sustains BP during standing, is relatively unaffected, if not spared, in PSP. These findings increase our understanding of the clinical signature of PSP and have the potential to improve diagnostic accuracy in atypical parkinsonisms

by distinguishing PSP from the  $\alpha$ -synucleinopathies. Given our findings, this lack of correlation could also be true of other tauopathies. Further studies are warranted in determining whether nOH is absent in other tauopathies.

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## **Effect of laughter yoga and *Mucuna pruriens* seeds in Parkinson's disease patients in West Delhi population**

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**Objectives:** Laughter has been shown to generally improve mood in physically healthy adults, and specifically in adults with heart disease or cancer, but little research exists regarding the impact of laughter in adults with Parkinson's disease (PD). *Mucuna pruriens* (Mp) has been prescribed in Ayurveda for various brain ailments including inflammatory, antioxidant, hypoglycemic or PD. To study new methods of controlling Parkinson's disease complications by laughter yoga with Mp seed powder in PD patients in south Delhi metro population.

**Methods:** For this purpose, we used laughter yoga, which includes respiratory laughing and fun exercises. Using a cross-sectional design, which includes age, family history of PD, exercise status and waist circumference, fasting glucose & insulin, glucose tolerance test (GTT), and glycosylated hemoglobin (HbA1c), MRI, CT scan were recorded for 55 aging patients (subject) between 60-75 years old. A 30-minute lecture was followed by 30-minute intense laughing workout for those participants who had laughter yoga included in the program. After laughter yoga session, 30 gm of Mp seeds powder was given orally to all patients daily for one month.

**Results:** After 30 days treatment there were significant changes in glucose, insulin and glycosylated haemoglobin levels, MRI compare to normal levels with changes in life style and increase movement in body with laughter yoga and Mp seed powder treatment. Present study highlight that the successful treatment of PD patients not only requires drugs; but also family care, life style education, harmonised mind-body-soul, preventive approach toward activity of daily living.

**Conclusions:** Our study indicated the importance of daily opportunities for laughter yoga with Mp seed powder in patients with PD. The results of such studies will be useful for delaying of the aging process and development of new drugs for PD and age-related disorders.

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**Protective effects of Omega-3 PUFAs against impaired motor behavior induced by central administration of Manganese in mice**R. El Fari<sup>1</sup>, A. El Got<sup>2</sup>, H. Gamrani<sup>1</sup>*<sup>1</sup>University of Marrakech, Faculty of Science Semlalia, Biology, Marrakech, Morocco, <sup>2</sup>Université Hassan Premier Institut Supérieur des Sciences de la Santé-Settat (I3S), Settat, Morocco*

Manganese (Mn) is a metallic Trace element responsible for normal operation of several vital functions, it is actually implicated in the normal growth, in the immune response and operating as a cofactor for many enzymes particularly in the central nervous system which explains its key role in the neurotransmission.

Conversely exposition to immoderate levels of manganese induces poisoning, showing symptoms similar to Parkinson's disease so-called manganism. Animal models of Mn exposure are very delicate to study given the variable effects according to the doses, frequencies, administration modes and Mn forms floating from preventive to toxic effects.

Thus our study aimed to study the effects of central injections of 1,3,5 and 10µg of Mn in saline 0.9%, within the Striatum, Substantia nigra compacta and the lateral ventricle, along with the assessment of protective effects of Omega-3 PUFAs on the neurobehavioral level. results so far showed a deterioration of cognitive functions in the lowest doses and impairment of locomotor behavior, while pressing that Omega-3 PUFAs exert a significant neuroprotective effects in all cases.