ABSTRACT E-BOOK

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Grand Parade of Movement Disorders Video Challenge

V01
Dystonic dysarthria as a presenting feature of Wilson's disease

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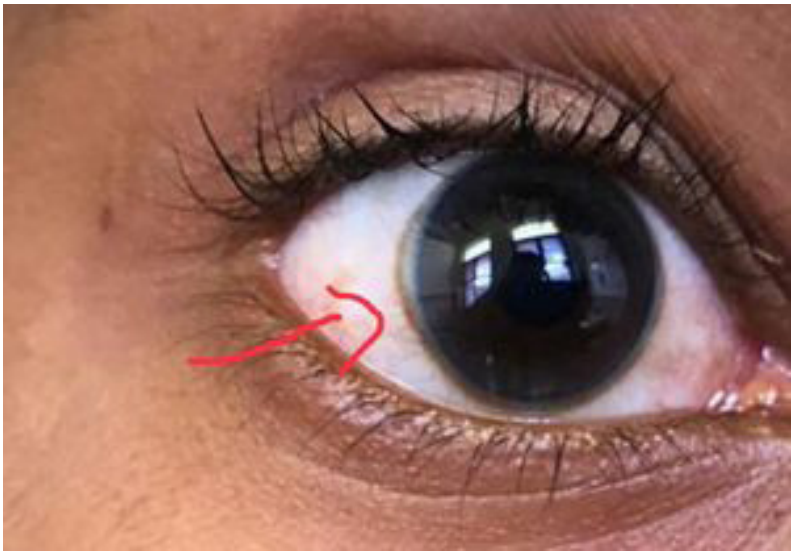
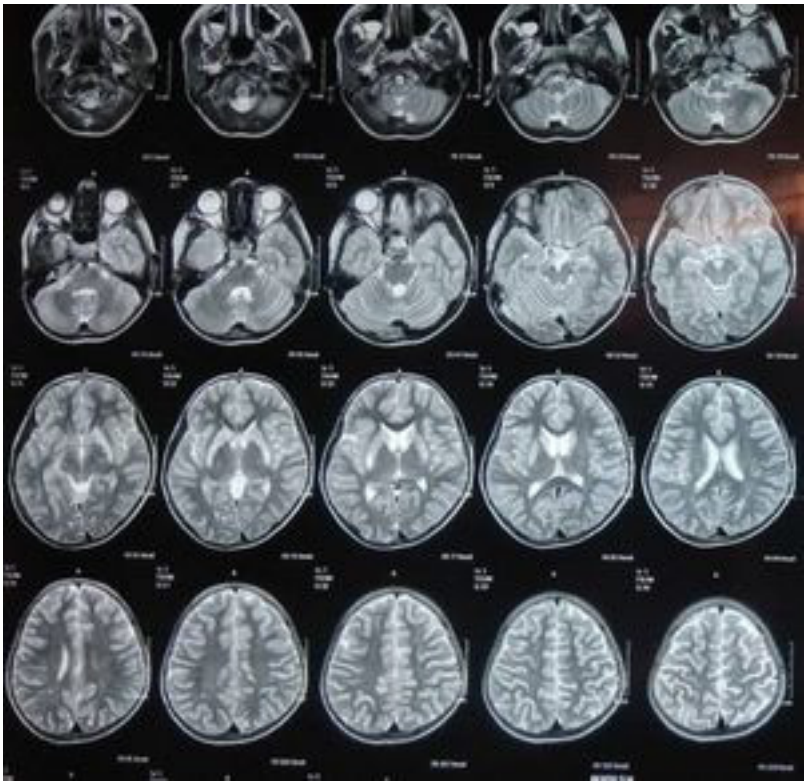
Background: Wilson's disease which is a rare genetic disorder, characterized by copper deposition in liver and brain, can present with a myriad of neurological manifestations including a wide range of movement disorders. Isolated dystonic dysarthria, as a presenting feature of Wilson's disease is very uncommon. Here we report a case of a 9 year old boy who had isolated dystonic dysathria at presentation.

Methods:





The patient was brought to our out patient department , with the baffling complaints of isolated, sub acute onset, insidiously progressive speech difficulties since 1 month. Examination revealed isolated dystonic dysarthria(video) and KF rings [Figure 1].MRI showed bilateral basal ganglia signal hyperintensities[Figure 2] . Serum ceruloplasmin was less than 9.5 mg/dl (Ref 20-60mg/dl) , 24 hour urinary copper levels were 64.48 mcg (20-60 mcg/day) and a diagnosis of Wilson's disease was made.

Results: After the diagnosis of Wilson's disease was established, child underwent detailed gastroenterological evaluation and was treated with zinc and D-penicillamine, subsequently showed clinical improvement.

Conclusions: This case highlights a lesser known presenting clinical feature of Wilson's disease. Here, the KF ring was a diagnostic clincher which guided a focused set of investigations leading to a successful diagnosis.

V02
Co-occurrence of Anti NMDA encephalitis - Covid-19 infection: A casual or causal association?

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Background: The major focus regarding the 2019 global coronavirus disease pandemic has been on cardiovascular and pulmonary complications. However, neurological impact have emerged as an increasingly recognized area of morbidity and mortality . It seems that COVID 19 could be another trigger factor for immune-mediated encephalopathies.
Methods: Consent was obtained to be able to be filmed and later reported in the scientific community
Results: An 18 Yo woman started with fever and respiratory symptoms. She tested positive for Covid-19 and after performing a normal chest tomography was sent home to carry out the quarantine. 7 days after diagnosis, started with behavioral changes, irritability and dystonic-type motor phenomena associated with falls.
She was admitted to the hospital. A brain MRI was performed, with normal results. The EEG showed global lentification without paroxysms. Laboratory with normal biochemical and immunological profile. Negative HIV and VRDL serology. Normal peripheral blood smears. Lumbar puncture with 3 cells, increased proteins with a value of 0.49 g/l, negative PCR for neuroviruses.
Given the suspected diagnosis of immune-mediated encephalopathy obtaining a positive result for NMDA antibodies in the two samples.
Immunoglobulin 2 g/kg was started. The patient showed an initial improvement in both motor and cognitive-behavioral aspects. One month after the first dose of immunoglobulin, she relapsed with reappearance of symptoms and the need to restart treatment.
Conclusions: There are reports of the association between NMDA and Covid 19 as an immunological phenomenon triggering encephalitis, probably associated with the inflammatory storm. This would be an example of neurological symptoms linked to SARSCOV2 infection

Blood and CSF analysis	
Blood	
RBC	4.05/mm^3
WBC	5,8x10_9/L
PLT	250.000/mm^3
ANA	negative
ANCAc	negative
ANCAp	negative
Anti-Ro	negative
Anti-La	negative
C	normal
T	normal
antibodies	NMDA +
CSF	
C	3/ml
P	0.49 gr/l
PCR virus	negative
OCB	type I
antibodies	NMDA +

RBC: Red blood count. WBC: White blood count. PLT: Platelet count. ANA: Antinuclear antibodies. ANCA: Anti-neutrophil cytoplasmic antibodies. C: complement. T: thyroid.

C: cells. P: proteins. OCB: oligoclonal bands.

[Table 1.}

V03
Negative motor phenomena in patients with Gilles de la Tourette syndrome

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Background: Patients with Gilles de la Tourette syndrome (GTS) may experience negative motor phenomena in the form of brief, recurrent cessations of motor output. We aimed to present the similar clinical pictures resulting from different underlying causes of motor inhibition in GTS patients.
Methods: We present two GTS patients with negative motor phenomena. Video 1: Patient with GTS - blocking tics as a part of multiple motor tics. Video 2: Patient with GTS and comorbid obsessive-compulsive disorder (OCD) - motor inhibition as a result of compulsions.
Results: The first video shows a patient with numerous complex clonic tics and additionally brief and sudden blocking tics. The inhibition of motor activity is involuntary and is a consequence of violent tics.
The second video shows a patient in which sudden and long-lasting cessations of motor output belong to voluntary movements. The patient has a sudden need to immediately perform certain activities in a planned, specific way, in order to feel that he is doing it "just right". This results in the interruption of the current activity in order to perform the set of ritualistic mental and motor behaviors.
Compulsion behaviors consist of tapping fingers on the cheek an even number of times, head movements, and contracting the back muscles in a scheduled manner until it feels painful. Only after performing these mental and motor rituals does the patient feel that he can continue previously interrupted activity or start the next one.
Conclusions: Blocking phenomena may be related to tic or OCD phenomenology. It is important for clinical practice to differentiate the underlying causes of negative motor phenomena in patients with GTS. Both pharmacological treatment and behavioral interventions are different for tics and obsessive-compulsive disorder.

V04
COVID-19 related two video-accompanied cases of severe ataxia-myoclonus syndrome

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Background: Pandemic state of COVID -19, now lasting more than 1 year resulted in a new clinical manifestations and neurological post-infection syndromes of SARS-CoV-2 infection. Recently, several papers reported ataxia-myoclonus syndrome following SARS-CoV-2 infection.
Methods: We present a video accompanied two new cases with ataxia-myoclonus syndrome following SARS-CoV-2 infection and discuss previously reported patients
Results: Ataxia-myoclonus syndrome, isolated myoclonus, opsoclonus-myoclonus syndrome as post-COVID-19 syndrome following infection were described in 16 patients (including our 2 cases). Patients were treated with intravenous immunoglobulins and/or steroids except for 4 patients, resulting in a significant improvement within a 1 week-2 months.
Conclusions: The increasing number of patients with the similar symptomatology shows that there may be a significant relationship between COVID-19 infection and ataxia-myoclonus syndrome. The subacute onset of neurological symptoms after resolved COVID-19 infection and prominent response to immunotherapy may suggest that the neurological manifestations are immune-mediated. As the recovery is highly possible, however it may take several weeks/months one should be aware of this diagnosis and beneficial effects of immunological treatment administered as soon as possible.

BEST Abstracts

Imaging and Biomarkers

BA01
Diffusion tensor imaging of the corticospinal tract: A marker for prodromal Parkinson's disease?

L.J. Pimer[1], M.N. Khan[2], J.R. McKelvey[3], A.J. Newman[4], G. Phillips[5], H.A. Robertson[1,3,6], T.M. Rolheiser[1], K. Schoffer[3], K.P. Good[1,4]

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Background: Parkinson's disease (PD) is typically diagnosed when motor symptoms first occur. However, PD-related non-motor symptoms may occur several years before diagnosis. REM sleep behaviour disorder (RBD) is a risk factor for developing PD in the future. Yet, being diagnosed with RBD is not sufficient to detect PD in its early stages and non-motor symptoms, such as olfactory deficits, and brain imaging markers may help to early identify PD in RBD patients.

Although some inconsistencies exist, the microstructure of the corticospinal tract (CST) has been shown to be altered in PD patients, but it is unclear whether RBD patients show similar abnormalities. This study examined whether idiopathic RBD patients show early signs of PD by assessing olfactory functioning and the CST with diffusion tensor imaging (DTI).

Methods: DTI data was collected on a 1.5T MRI scanner and the CST was tracked with probabilistic tractography (with seed regions in the bilateral primary motor cortex and mediolateral cerebral peduncles). Olfactory functioning was assessed with the University of Pennsylvania Smell Identification test (UPSIT). Idiopathic RBD patients (n = 24) were compared to early PD patients (n = 26) and age- and sex-matched healthy controls (HCs; n = 24) on DTI metrics (FA, MD, AD, and RD) of the bilateral CST and UPSIT scores.

Results: RBD patients showed significantly higher mean diffusivity values of the right CST compared to HCs ($p < .05$). RBD and PD patients had significantly lower UPSIT scores than HCs. There were no other significant differences in DTI metrics or UPSIT scores between the groups. **Conclusions:** The combination of RBD and olfactory deficits may prove to be the most potent marker for the development of PD; however, while abnormal microstructure of the right CST is related to RBD, it does not seem to be an early marker of PD patients without comorbid RBD.

Parkinson Disease: Clinical assessment (including devices)

BA02
Prevalence of Vitamin D, B1, B6, and B12 deficiencies in Parkinson Disease and associations with nutrient intake

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Background: Vitamin deficiencies can lead to cognitive loss, hallucinations, neuropathy, falls, gait disturbances, weakness, bone fragility and fractures, and poor quality of life. Parkinson disease patients can exhibit these symptoms due to disease status, but the contribution of nutrient deficiencies to these symptoms is unknown. This study was conducted to evaluate the frequency and associations of deficiencies of vitamin B1, B6, B12 and D with nutrient intake in a Comprehensive Parkinson Disease Clinic (CPDC) at the University of Nebraska Medical Center.

Methods: Consented subjects completed a Harvard food frequency questionnaire (FFQ) for quantification of dietary intake. Serum levels of vitamin B1, B6, B12 and D collected for clinical use were obtained from the medical record. Frequencies of deficiency were calculated and associations between intake and serum levels were analyzed. A p-value of < 0.05 was considered statistically significant.

Results: There were 169 subjects included in the final analysis. Prevalence of vitamin deficiencies were as follows: 36.0% were deficient in vitamin D (25(OH)D levels $\leq$ 30 ng/ml), 25.9% were deficient in vitamin B6 ($\leq$ 20 nmol/L), 6.5% were deficient in vitamin B12 ($\leq$ 200 pg/mL), and. 6.1% were deficient in vitamin B1 ($\leq$ 70 nmol/L). Those with serum deficiencies of vitamins B1 and D had significantly lower intakes than those with normal levels ($p = 0.02$, $p = <0.001$, respectfully).

Conclusions: Deficiencies in vitamins B1, B6, B12, and D occurred at high frequencies in this cohort, ranging from 6.1-36.0%. Prevention of these deficiencies can occur only if recognized. *Treatable signs and symptoms of nutrient deficiencies can masquerade as worsening of Parkinson Disease and can easily be missed.*

BA03

Early versus later levodopa and onset of motor fluctuations in PD: Observations from the Parkinson's outcomes project

S.Y. Chiu[1], *A. Ramirez-Zamora*[1], *B. Patel*[1], *S.S. Wu*[2], *H. Gao*[2], *O.T. Nguyen*[1], *I.A. Malaty*[1]
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Background: Optimal timing of levodopa initiation remains controversial. Early use may improve quality of life, but fear of motor complications such as levodopa-induced dyskinesia delays utilization. We aimed to characterize patients with early versus later levodopa exposure, defining "early" as within 2 years of Parkinson's disease (PD) diagnosis, and to determine whether early exposure influences onset of motor complications.
Methods: To explore association between time of levodopa initiation and onset of motor complications, we analyzed data from the Parkinson's Foundation Parkinson Outcomes Project, a large prospective multicenter database quality improvement initiative involving worldwide expert centers. We identified patients entering the study within 2 years of diagnosis, had PD diagnostic certainty >90%, and were followed for ≥3 years. We compared baseline demographics, clinical features, and time to motor complications between those with early versus later levodopa exposure.
Results: We identified 738 patients of which 67% had early levodopa (n=491). Early users were exposed to levodopa within a mean of 1.4±0.7 years since PD diagnosis, compared to 4.5±1.5 years in later users (p<0.001). Early users were older (mean age 66±10 vs. 61±8 years, p<0.001), had longer disease duration (3.5±3.1 vs. 2.9±2.2 years, p<0.01), and worse PDQ39-mobility, cognitive, and Hoehn and Yahr (HY) scores at baseline (all p<0.05). After controlling for demographics, HY stage, disease duration, and comorbidities, early levodopa was associated with earlier time to development of motor complications (mean 3.5±2.3 years vs. 5.2±2.5 years; median 4.0 vs. 6.0 years, hazard ratio 2.2, p<0.0001). Older age and higher HY stage at baseline were associated with earlier development of motor complications. 99.6% of patients had motor complications by 11 years of diagnosis.
Conclusions: In this cohort, early levodopa exposure (within 2 years of PD diagnosis) was associated with earlier onset of motor fluctuations, controlling for disease duration.

Parkinson Disease: Therapy (excluding surgical, physical)

BA04
Preclinical development of brain-penetrant structurally targeted allosteric regulators for the treatment of GBA1 Parkinson's disease and related α-synucleinopathies

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Background: Homozygous and heterozygous mutations in the GBA1 gene encoding the lysosomal enzyme b-glucocerebrosidase (GCase) represent the most common risk factor for Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Of relevance to these disorders is the interaction between GCase and alpha-synuclein (α-syn), as there appears to be an inverse relationship between GCase and α-syn levels. Indeed, reduced GCase is associated with increased α-syn accumulation as well as a change from its soluble form to its aggregate form, and it has been postulated that α-syn accumulation in lysosomes may reduce overall GCase activity. These findings suggest that decreased GCase activity may contribute to pathogenesis in many forms of PD, and therefore activating mutant and wild-type GCase may represent a potential therapeutic strategy.
Methods: Gain Therapeutics has applied its innovative proprietary drug discovery platform, Site-directed Enzyme Enhancement Therapy (SEE-Tx™), to the development of small-molecule structurally targeted allosteric regulators (STAR^S) that can allosterically bind and stabilize GCase thus avoiding its degradation and recovering its enzymatic activity.
Results: Here we report recent advancements in the development of orally bioavailable and brain penetrant lead STAR^S, which have shown promising effects in different models of PD. Indeed, they enhance GCase enzymatic activity in a dose-dependent manner. This effect was achieved on WT and mutated GCase in patient-derived fibroblasts as well as on WT GCase in C57BL/6 mice. They also show neuroprotective effects and/or α-syn reduction in CBE- and rotenone-induced in vitro models. Most importantly, similar IHC results were obtain after compound treatment in a rotenone-induced murine model and supported the behavioral changes, i.e. improved locomotion, observed in vivo.
Conclusions: Altogether, the allosteric regulators identified with the proprietary SEE-Tx™ drug discovery platform support the restoration of key biological activities found to be impaired in GBA1-related synucleinopathies, thus warranting further development towards the clinic.

BA05
Baseline characteristics do not predict time to discontinuation of levodopa-carbidopa intestinal gel infusion in patients with Parkinson's disease

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Background: Enteral infusion of levodopa-carbidopa intestinal gel (LCIG) is a well-established therapy for patients with advanced Parkinson's disease. Treatment effectiveness varies between patients as reflected by differences in time to discontinuation, ranging from a few months to more than 10 years. To optimize patient selection, it is important to have knowledge of baseline characteristics influencing time to discontinuation. Potentially, such knowledge may lower the number of patients discontinuing LCIG early.
Methods: A retrospective cohort study was performed in 4 Dutch hospitals. In December 2019, we reviewed the medical files of 205 consecutive patients who started treatment with long-term LCIG in the period January 2005 - December 2016 (57.1% male; mean age: 66.2 years; mean disease duration: 12.2 years). Time to discontinuation was studied using Kaplan-Meier analyses. Baseline patient characteristics were used as covariates in Cox regression models.
Results: During a mean follow-up of 4.3 years 43 patients (21%) discontinued, while 66 patients died during follow-up (31%); the cause of death was not related to LCIG therapy. The estimated mean time to discontinuation was 9.5 years (95% CI: 8.7-10.3). No baseline patient characteristics were statistically significantly associated with time to discontinuation. Of note, higher age at initiation was not a risk factor for early discontinuation (HR for age: 0.97; 95% CI 0.93 -1.00; $p = 0.064$). Patients who stopped LCIG infusion had a significantly higher rate of hospitalizations compared to patients continuing therapy.
Conclusions: The discontinuation rate of LCIG was low. Many patients continued LCIG until death. Baseline characteristics do not help in defining the optimal patient profile for LCIG. Complications during therapy seem to be more decisive for time to discontinuation of LCIG and, thus, treatment effectiveness.

Parkinson Disease: Other topics

BA06
Long-term safety and efficacy of apomorphine sublingual film for the treatment of "OFF" episodes in patients with Parkinson's disease

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Background: In a 12-week pivotal study, apomorphine sublingual film (APL) was efficacious and generally well-tolerated for on-demand treatment of "OFF" episodes in patients with Parkinson's disease (PD). Herein, we evaluated long-term safety (LTS) and efficacy of APL.
Methods: An ongoing, open-label, Phase 3 study (NCT02542696) enrolled patients with PD and "OFF" episodes. Patients were required to be on stable PD medication regimens. APL dose titration occurred during practically defined "OFF" to determine the dose (10–35 mg; 5-mg increments) that converted patients to FULL "ON" by 45 minutes. In the LTS phase, patients self-administered their titrated APL dose for ≤5 "OFF" episodes/day. Endpoints included TEAEs (primary), change from predose in MDS-UPDRS Part III score, and percentage of patients with a self-rated FULL "ON" within 30 minutes postdose.
Results: Interim (data cut May 2019) analyses included 425 (safety) and 345 (efficacy; median exposure to APL [LTS phase]: 141 days) patients. In the safety population, TEAEs occurred in 84% of patients and were mostly mild (66%); the most common (≥10%) included nausea (27%), yawning (12%), dizziness (11%), and somnolence (11%). Common oral TEAEs (≥5%) included mucosal erythema (8%). Syncope occurred in 2% of patients. TEAEs leading to discontinuation occurred in 31%; the most common (≥2%) were nausea (6%), lip swelling (3%), and dizziness (2%).
There were 4 deaths; none were considered drug-related. At week 24, mean changes from predose in MDS-UPDRS Part III scores at 15, 30, and 60 minutes were –13.3, –20.1, and –19.2, respectively, with similar results at weeks 36 and 48. FULL "ON" by 30 minutes postdose was observed in 74%, 89%, and 84% at weeks 24, 36, and 48, respectively.
Conclusions: Interim results (≤48 weeks) support LTS and efficacy of apomorphine sublingual film as an on-demand treatment of "OFF" episodes in patients with PD.

BA07
Comparison of gastrointestinal transit times in typical and erratic levodopa-responders in patients with Parkinson's disease

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Background: Simultaneous measurement of regional and Whole Gut Transit Time along with levodopa level is a crucial step in understanding the effect of motility disorders and their location on changes to response to levodopa.
Methods: 10 PD patients with typical levodopa response (predictable fluctuations) and 10 erratic responders (sudden "ON"/"OFFs", delayed time to "ON", or response failure) will ingest SmartPill, a wireless motility capsule that measures transit time in GI tract. Serum levodopa levels every 30 minutes and serial finger tapping for the first three hours of SmartPill and their first dose of Levodopa ingestion will be used to study the correlation between changes in GI motility and response and T-max of levodopa. The presence or absence of small intestinal bacterial overgrowth (SIBO) will be documented by a glucose breath test.
Results: Fifteen patients (9 women, 6 men; mean age 68), including 8 erratic and 7 typical responders, have completed the study. Serum levodopa level in erratic responders had more than one peak whereas typical responders had their highest serum levodopa level at 30 minutes after taking their morning dose with a subsequent gradual decrease in their level. It took 120 minutes for >80% of the erratic responders to feel ON compared with 60 minutes for the same percentage of typical responders to feel ON. No SIBO negative patient had abnormal Small Bowel Transit Time (SBTT), while 60% of SIBO positive patients had abnormal SBTT. Two erratic responders had abnormally long SBTT and one typical responder had abnormally short SBTT.
Conclusions: Erratic responders displayed an erratic pattern in serum levodopa levels and delayed onset of feeling ON, whereas typical responders had one early peak and a gradual decrease in their level and an earlier onset of ON time. SmartPill is a feasible technology to assess transit time in PD patients.

Other Parkinsonian Disorders

BA08
Associations of mitochondrial genomic variation with risk of dementia and Lewy body disease and disease severity

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Background: Lewy body disease (LBD) is a heterogenous group of disorders where clinical presentations include dementias and parkinsonian phenotypes. Neuropathologically, LBD are predominantly characterized by aggregates of alpha-synuclein proteins (Lewy bodies; LB). The genetic etiology of LBD is complex and mitochondrial dysfunction has been observed.
The aim of this study was to investigate if mitochondrial genomic (mtDNA) background effects risk of developing clinical Dementia with Lewy bodies (DLB) or neuropathologically-confirmed LBD and their neuropathological measures.
Methods: 360 clinical DLB cases, 446 neuropathologically-confirmed LBD cases with a high likelihood of having DLB (LBD-hDLB), and 910 neurologically healthy clinical controls were genotyped for 39 unique mtDNA haplogroup-defining variants, and mtDNA haplogroups were assigned. Neurofibrillary tangles, senile plaques, LB counts and distribution, substantia nigra neuronal loss, and striatal dopaminergic degeneration were also assessed across multiple brain regions in LBD-hDLB cases.
Association tests of mitochondrial haplogroups with risk of clinical DLB and LBD-hDLB were examined using logistic regression models adjusted for age and sex. Additionally, individual neuropathological measures were assessed against mitochondrial haplogroups in LBD-hDLB cases, using age at death and sex-adjusted regression models.
Results: No mtDNA haplogroups were statistically significantly associated ($P<0.0024$) with risk of clinical DLB or LBD-hDLB in case-control analysis, but haplogroup H background suggested reduced risk of clinical DLB (OR=0.61, P=0.006).
Furthermore, no statistically significant associations were observed between mtDNA haplogroups and neuropathological outcomes, but again, haplogroup H suggested to reduce ventrolateral neuronal loss (OR=0.44, P=0.033).

Conclusions: Mitochondrial haplogroup H background may be protective against developing DLB, which may be influenced by reduced neuronal loss in ventrolateral regions. Further validation in larger clinical and neuropathological cohorts with detailed phenotype or quantitative measures is warranted.

Gait and Other Movement Disorders

BA09
Efficacy of a 6-week brisk walking program in improving gait speed and arm swing in people with Parkinson disease

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Background: Brisk walking is moderate-intensity aerobic exercise involving fast speed training with large steps and big arm swing. Previous study indicated that a 6-week brisk walking program increased balance and motor performance walking capacity up to 6 weeks post-training in people with early Parkinson's disease (PD) (Wong-Yu et al., 2019). It is worthy to investigate whether additional benefits are evident in gait and arm swing outcomes.
The objective was to examine whether 6-week brisk walking program would be effective in improving gait and arm swing parameters in people with PD at post-training.
Methods: Eligible participants were randomly allocated into experimental (EXP) or upper limb group (CON). EXP group received brisk walking using smart watch heart rate monitor (at 40-60% heart rate reserve), while CON group practiced upper limb exercises. Participants attended six 90-minute training sessions weekly under physiotherapy supervision, and performed home exercise twice weekly for 6 weeks to reach a total of 150 minutes weekly exercise time post-training. Instrumental walk test of APDM Movement Monitoring inertial sensor system was used to measure outcomes including stride length, gait speed and peak arm swing velocity at comfortable speed.
Results: Seventy-three participants (40 EXP, 33 CON) completed six training sessions. Significant group*time interactions were found for all outcomes using 2-way ANOVA. Immediately post 6-week training, only the EXP group significantly increased the stride length (+0.02m, $p<0.05$), gait velocity (+0.03m/s, $p<0.05$), and peak arm swing velocity (+9.3 deg/s, $p<0.05$) from baseline. The 6-week attendance was 98.4% and no adverse effects were reported during the training period in EXP group.
Conclusions: The brisk walking program enhanced stride length, gait and arm swing velocities in people with PD at 6-week post-training. Further study will be conducted to investigate the long-term effects of this program.

BA10
IncobotulinumtoxinA for upper- or combined upper- and lower-limb spasticity in children and adolescents with cerebral palsy: Phase 3 XARA study

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Background: This study assessed efficacy and safety of incobotulinumtoxinA for upper-limb (UL) and combined UL/lower-limb (LL) spasticity in ambulant and non-ambulant children and adolescents with cerebral palsy (CP).

Methods: XARA (NCT02002884) was a randomised, phase 3 study with a double-blind main period (MP) and open-label extension (OLEX) period. Patients aged 2–17 with uni- or bilateral CP and Ashworth Scale (AS) score ≥2 for the main clinical target patterns, flexed elbow and/or flexed wrist, were enrolled. Patients were randomised (2:1:1) to three incobotulinumtoxinA dose groups (8, 6, 2 U/kg body weight [BW]; maximum 200, 150, 50 U/UL) with additional LL injections (total body dose ≤16–20 U/kg BW [≤400–500 U], depending on Gross Motor Function Classification System level [GMFCS]). Patients received three further injection cycles (ICs) in the OLEX, with doses per the 8 U/kg BW group. Outcomes included AS, Global Impression of Change Scale (GICS) and adverse events (AEs).

Results: Overall, 350 patients (62.9% male, mean [SD] age 7.3 [4.4] years, BW 25.0 [15.0] kg, 30.9% GMFCS IV–V) were treated; 281 (80.3%) completed the study, receiving four incobotulinumtoxinA ICs. In the MP, AS scores for the UL main clinical pattern improved significantly from baseline to Week 4 ($p<0.0001$, mixed model repeated measures [MMRM]), with a significantly greater improvement in the 8 U/kg versus 2 U/kg dose group ($p=0.017$, MMRM). Improvements were observed in all treated UL/LL clinical patterns and across all OLEX ICs. GICS scores confirmed global improvements in UL/LL spasticity, but did not differ between dose groups. AE incidence did not increase with increasing dose or repeated treatment.

Conclusions: Data from this study show the efficacy and safety of incobotulinumtoxinA for muscle tone reduction in multipattern treatment of spasticity in patients with CP (GMFCS I–V).

Funding: Funded by Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany.

Poster

Basic Neuroscience (excluding Genetics)

P01
Parkinson's disease–associated VPS35 mutant reduces mitochondrial membrane potential and impairs PINK1/Parkin-mediated mitophagy

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Background: Mitochondrial dysfunction plays a prominent role in the pathogenesis of Parkinson's disease (PD), and several genes linked to familial PD, including *PINK1* and *PARK2*, are directly involved in processes such as mitophagy that maintain mitochondrial health. The dominant p.D620N variant in *VPS35* has also been associated to familial PD but has not been functionally connected to *PINK1* and *PARK2*.
Methods: To better mimic and study the patient situation, we used CRISPR-Cas9 to generate heterozygous human SH-SY5Y cells carrying the PD-associated D620N variant in *VPS35*. These cells were treated with the protonophore CCCP to induce PINK1/Parkin-mediated mitophagy, which was assessed using biochemical and microscopy approaches.
Results: Mitochondria in VPS35-D620N cells exhibited reduced mitochondrial membrane potential and appeared to already be damaged at steady state. As a result, the mitochondria of these cells were desensitized to CCCP-induced collapse in mitochondrial potential, as they displayed altered fragmentation and were unable to accumulate PINK1 at their surface upon this insult. Consequently, Parkin recruitment to the cell surface was inhibited and initiation of PINK1/Parkin-dependent mitophagy is impaired.
Conclusions: Our findings extend the pool of evidence that the p.D620N mutant VPS35 causes mitochondrial dysfunction and suggest a converging pathogenic mechanism between VPS35, PINK1 and Parkin in PD.

P02
Neuronal cells immunological response exercebates Neurodegeneration

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Background: The role the immune system plays in the central nervous system is becoming increasingly interesting, as the brain, previously regarded as immune-priviledge site, is now known to exhibit immunological responses to infections and other foreign materials. The studies of neurodegenerative diseases focus on neurons and their networks; however, immunological processes are known to arise alongside degenerating neurons.
This review aimed to clarify, the role innate immunity plays in Neurodegeneration.
Methods: The biology of microglia, the brain immune cells, play in the maintainance of a healthy brain environment was reviewed, alongside it's role in neuroinflammation, which is the Hallmark of neurodegenerative diseases. The functions of the blood-brain barrier was also studied, as compromise to the semi-permeable structure is responsible for the infiltration of peripheral immune cells to the brain; plus the integrity of the reactive microglia, astrocytes and pericytes during infections.
All these led to the understanding that secretion of inflammatory mediators, chemokines and cytokines like Tissue Necrotic Factor-alpha, interleukin 1 beta, interferon-gamma and some Cytotoxic factors such as superoxide radicals, nitric oxide and reactive oxygen species, happen in response to microbial infections.
Results: Pro-inflammatory molecules like cytokines and chemokines are known to promote the formation of paracellular gaps during neuronal immunological response to infection or foreign particles. During these processes, Matrix metalloproteases are also released, which degrade proteins present in the extracellular matrix and these may contribute to the loss of the pericytes. It was observed that the events leads to increase in the permeability of the Blood-Brain Barrier and invasion of peripheral immune cells.
Conclusions: Neurodegenerative disease are characterized by misfolding of proteins such as alpha synuclein and tau proteins in Parkinson's and Alzheimer diseases respectively. These misfolded aggregates are toxic to the cells and it is observed that neuroinflammatory cascades are linked to the protein aggregation leading to Neurodegeneration.

P03
Gut microbiota composition of treatment-naïve de novo Parkinson's Disease patients

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Background: Over fifteen independent studies have demonstrated gut microbial dysbiosis in Parkinson's disease (PD) subjects. However, the interpretation of these findings is hampered as almost all included PD subjects already used dopaminergic medication. In addition, participants were often included several years after diagnosis. Here, the gut microbiota composition of newly diagnosed, treatment-naïve PD subjects of the Dutch Parkinson Cohort (DUPARC) will be compared to age- and sex-matched healthy controls (HC).

Methods: Partial 16S rRNA-gene sequencing was performed on stool samples of 140 treatment-naïve *de novo* PD and 85 HC. In addition, our own control group will be supplemented with non-PD subjects included in LifeLines DEEP, a population-based cohort study with participants from the same Dutch region as the DUPARC participants. Sampling, DNA extraction and sequencing protocols were the same as in LifeLines DEEP.

Primary endpoint is the gut microbiota composition based on 16S rRNA-gene sequencing. Additionally, the Unified Parkinson Disease Rating Scale, the Non Motor Symptoms Questionnaire, the Montreal Cognitive Assessment, a dietary diary and a stool diary were assessed as secondary endpoints relevant for either the gut microbiota composition or the clinical status of the participant.

Results: Preliminary analysis of our own recruited de novo PD and HC samples suggests a statistically significant difference in overall gut microbiota community (i.e. Beta diversity) adjusted for age and sex (p=0.0128). Overall gut microbiota community structure and differential abundance analyses of the entire dataset, adjusted for additional relevant confounders, will be presented at the congress.

Conclusions: This is the largest gut microbiota composition study in treatment-naïve de novo PD subjects. Consequently, the first, well-powered inquiry of the gut microbiota composition during the early stages of PD can be conducted, without the putative confounding influence of dopaminergic medication.

P04
Modeling of Parkinson's disease at the early stage as a tool for studying the mechanisms of neuroplasticity

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Background: Parkinson's disease (PD) is characterized by long-term degeneration of nigrostriatal dopaminergic neurons without motor symptoms, which is apparently explained by compensatory processes. The study was aimed to evaluate compensatory processes in the nigrostriatal system at modeling PD at the early stage.
Methods: PD at the early stage was modeled in mice by double administration with 2 hours interval (single dose, 6 mg/kg) of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).
Then, within 24 hours, such indicators were assessed as:
(i) the number of tyrosine hydroxylase (TH)-immunoreactive neurons in the substantia nigra,
(ii) the number of axons containing only TH or only aromatic L-amino acid decarboxylase (AADC) and axons containing both enzymes (double-immunolabeling) in the striatum,
(iii) dopamine content and TH activity (L-DOPA content upon AADC inhibition) (HPLC) in the striatum.
Results: According to our data, only the striatum was changed in MPTP-treated mice. During the first 3-6 hours after MPTP administration, neurodegenerative processes predominate, which is manifested in a decrease in: TH activity, dopamine content, the number of bienzymatic and monoenzymatic TH-axons. Over the subsequent period (6-24 hours), compensatory processes predominate, which manifests in:
(i) an increase in TH activity,
(ii) stabilization of DA level,
(iii) an increase in the number of dopaminergic (bienzymatic) axons and monoenzymatic axons, which, as we showed earlier, synthesize dopamine in cooperation.
Conclusions: Our data suggest that the functional insufficiency of the nigrostriatal dopaminergic system at the early stage of PD is compensated by an increase in the number of dopaminergic and monoenzymatic axons, associated with an increase in axonal dopamine synthesis.

This project was funded by Ministry of Science and Higher Education of the Russian Federation (grant agreement № 075-15-2020-795 of 29.09.2020)

P05
Modeling the degradation of the nigrostriatal dopaminergic system for studying the molecular mechanisms of pathogenesis

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Background: Progressing degradation of the nigrostriatal dopaminergic system, which begins with striatal axons long before the onset of motor symptoms, is a key characteristic of Parkinson's disease (PD). This study aimed to develop a PD model of the early stage of degradation of the nigrostriatal system.
Methods: Mice received 4 injections of 12 mg/kg 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) each 2 hours, or saline. Then, for 24 hours, we estimated: the number of tyrosine hydroxylase(TH)-immunoreactive neurons in the substantia nigra (SN) and axons in the striatum, the content of dopamine and TH (protein), TH activity as L-DOPA accumulation upon inhibition of aromatic L-amino acid decarboxylase.
Results: Degradation (loss) of axons in the striatum begins immediately after MPTP administration and lasts 4 hours, which is accompanied by sharp decrease in dopamine content and low TH activity. Thereafter, the number of axons and dopamine content did not change. Stabilization of the dopamine level is due to a decrease in the TH content and increase in its activity from 6 to 12 hours. Axonal degradation leads to retrograde degeneration (loss) of nigral neurons within 3-6 hours after MPTP administration and a decrease in TH activity. Over the next 6 hours, TH activity increases and TH content decreases, resulting in an increase in dopamine content. By the 12th hour after MPTP administration, all morphological and functional parameters reach a plateau.

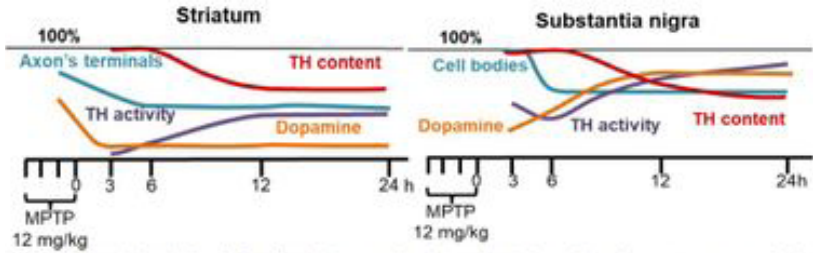

Figure. Morphological and functional changes in nigrostriatal dopaminergic neurons, axons in the striatum and bodies in the substantia nigra, in mice within 24 hours after MPTP administration.

Conclusions: The developed model reproduces the early PD pathogenesis: retrograde degeneration of dopaminergic neurons and compensatory processes leading to stabilization of dopamine neurotransmission.
This study was supported by RSF (project № 20-75-00110).

P06
Metabolism of sphingolipids in the nigrostriatal systemon the models of Parkinson's disease at the preclinical and clinical stages

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Background: Recent literature data suggest that the pathogenesis of neurodegenerative diseases, including Parkinson's disease (PD), is associated with changes in sphingolipid metabolism in the brain. The aim of this study was to evaluate the metabolism of sphingolipids in the nigrostriatal system in mice using original neurotoxic models of preclinical and clinical stages of PD.
Methods: PD at the preclinical and clinical stages was modeled in mice by a single (18 mg / kg) or triple (10 mg/kg with 2-hours interval between the injections) s.c. administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Two weeks after MPTP administration, animals were tested for motor behavior (open field test and rotarod). Then they were decapitated, and the striatum and substantia nigra were dissected. Dopamine (HPLC) and sphingolipids (ceramides, sphingomyelins, and sphingosine) (mass spectrometry) were measured in the striatum and substantia nigra.
Results: In mice, when modeling the preclinical stage of PD, there were no motor disorders, and the dopamine content in the striatum decreased by 60%. In the model of the clinical stage of PD, the dopamine content in the striatum decreased by 79%, which was associated with the impairment of motor behavior. As for sphingolipids, modeling of PD at both stages results in an increase in the content of sphingolipids in substantia nigra. This is due to an increase in the concentration of ceramides associated with fatty acids, such as C18: 1/14: 0, C18: 1/18: 0, C18: 1/24: 1, and monohexosylceamides associated with fatty acids such as C18: 1/18: 0 and C18: 1/24: 1. Unlike the substantia nigra, in the striatum - the site of projection of dopaminergic axons, no changes in the content of sphingolipids were detected.

Conclusions: Our data suggest that the metabolism of sphingolipids in the nigrostriatal system in PD patients, as in animal models changes not only at clinical stage but also at the preclinical stage.

Imaging and Biomarkers

P07
Differential inhibition of LRRK2 in Parkinson's patient blood by a G2019S selective LRRK2 inhibitor

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Background: A common genetic mutation that causes Parkinson's disease (PD) is the G2019S *LRRK2* mutation. A precision medicine approach that selectively blocks only excess kinase activity of the mutant allele could yield a safe and effective treatment for G2019S *LRRK2* PD. To determine the activity of a G2019S mutant selective LRRK2 kinase inhibitor as compared to a nonselective inhibitor in blood of subjects with genetic and idiopathic PD on two LRRK2 biomarkers; pSer935 LRRK2 and pThr73 Rab10.

Methods: Blood was collected from 13 subjects with or without a G2019S *LRRK2* mutation with PD and one healthy control. Peripheral blood mononuclear cells were treated ex vivo with a novel G2019S LRRK2 inhibitor (EB-42168) or the nonselective inhibitor MLi-2. Quantitative western immunoblot analyses were performed.

Results: EB-42168 was 100 times more selective for G2019S LRRK2 when compared to wild-type (WT) LRRK2. Concentrations that inhibited phosphorylation of pSer935 LRRK2 by 90% in homozygous G2019S *LRRK2* patients, inhibited pSer935 LRRK2 by 36% in heterozygous patients, and by only 5% in patients carrying only the WT allele. Similar selectivity was seen for pThr73 Rab10. MLi-2 showed an equivalent level of inhibition across all genotypes.

Conclusions: These findings demonstrate that EB-42168, a G2019S LRRK2 selective inhibitor, lowers mutant G2019S LRRK2 phosphorylated biomarkers while simultaneously sparing WT LRRK2. Selective targeting of G2019S LRRK2 with a small molecule lays the foundation for a precision medicine treatment of G2019S *LRRK2* PD.

P08
Neural correlates of risky decision making in Parkinson's disease patients with impulse control disorders

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Background: Approximately 6-15.5% of patients with Parkinson's disease (PD) experience impulse control disorders (ICDs), characterized by deficient voluntary control over impulses, drives, or temptations regarding excessive hedonic behavior.
The present study aimed to better understand the neural basis of impulsive, risky decision making in PD patients with ICDs by disentangling the decision and outcome mechanisms that can be dysfunctional in ICDs.
Methods: We collected fMRI data from 20 patients with ICDs and 28 without ICDs (classified using the QUIP questionnaire) performing an information-gathering task. Patients viewed sequences of bead colors drawn from hidden urns and were instructed to infer the majority bead color in each urn. With each new bead, they could choose to either seek more evidence by drawing another bead (draw choice) or make an urn-inference (urn choice followed by feedback). We manipulated risk via the probability of bead color splits (80/20 vs. 60/40) and potential loss following an incorrect inference ($10 vs. $0). Patients also completed the Barratt Impulsiveness Scale (BIS) to assess impulsivity.
Results: Patients with ICDs showed greater urn choice-specific activation in a variety of regions including the right middle frontal and angular gyrus, and bilateral temporal gyrus. Patients without ICDs showed greater probability-specific activation in cerebellar regions known to be involved in uncertainty processing, indicating that they considered probability more than patients with ICDs. Across all patients, fewer drawn beads* and higher BIS scores (i.e., more impulsivity) were associated with less parietal activation during both decision making and outcome processing, fitting prior indications that this area is associated with the amount of evidence-seeking. [*FWE-corrected $p<.05$; other results unc. $p<.0005$]
Conclusions: Our findings demonstrate that impulsiveness in PD is associated with substantial differences in neural processing of risk-related information and outcomes, particularly in parietal and cerebellar areas. These results provide a neurofunctional basis for developing targeted therapeutic interventions.

P09

Provocation test with monoiodotyrosine for the detection of latent nigrostriatal dysfunction in Parkinson's disease

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Background: Developing of early diagnosis of Parkinson's disease (PD) is still an emerging issue of the modern neuroscience. Numerous attempts to solve this problem evaluating the peripheral biomarkers remain unsuccessful.
The goal of this study was to apply another approach – pharmacological provocation test. It is based on a temporary reversible enhancement of the functional insufficiency of the degrading nigrostriatal dopaminergic system to a threshold for short-term manifestation of motor symptoms. As a provocative agent we propose monoiodotyrosine (MIT) – an inhibitor of dopamine synthesis, which is present in the body as thyroid hormones precursor.
Methods: Presymptomatic PD model was reproduced in mice with single subcutaneous injection of 18 mg/kg of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). One week later MIT (100 mg/kg) was administered subcutaneously to MPTP-treated mice or to saline-treated control. Dopamine was assayed in the striatum and substantia nigra by HPLC with electrochemical detection. Motor activity of mice was evaluated with an open-field test.
Results: Presymptomatic PD model was characterized by the absence of motor dysfunctions and subthreshold loss of striatal dopamine (Fig.1A,B). Administration of MIT didn't affect motor activity in control group, but caused motor impairment in MPTP-treated mice (Fig.1A) due to a threshold decrease of striatal dopamine (Fig.1B).

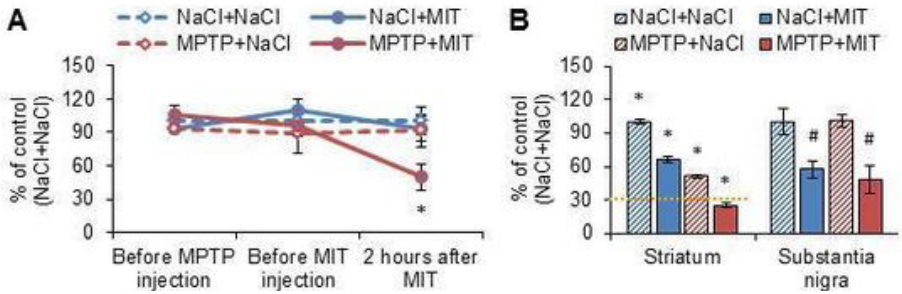

Figure 1. Total distance in open-field test (A) and dopamine content in the nigrostriatal system (B) 2 hours after MIT injection to MPTP-treated mice and control (saline).
** p<0.05 to all other groups, # p<0.05 to non-MIT groups (one-way ANOVA), orange dotted line - threshold for motor symptoms appearance*

Conclusions: Thus, we obtained an experimental proof that MIT could be used as a candidate provocative agent for the detection of latent nigrostriatal dysfunction in PD. The short-term and long-term safety of MIT-based provocation test are going to be evaluated in the future studies.

This research was supported by the Russian Science Foundation (project No.20-75-00034).

P10
MiR-29c-3p could be a biomarker for Parkinson's disease

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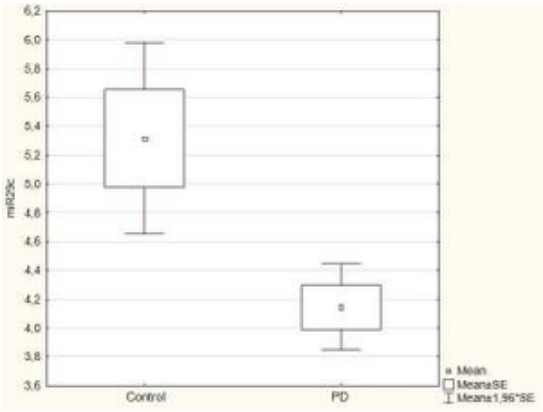
Background: Parkinson's disease (PD) is one of the most common movement disorders worldwide. Still, there is a lack of informative biomarkers for the exact diagnosis of PD. There is a growing interest in epigenetic alteration in PD last years. MicroRNAs, as one of the epigenetic regulators, showed changes in expression in the blood of patients with PD and in the control group. The aim of our study was to analyze the role of a set of microRNA as a potential biomarker of PD.

Methods: 40 patients with PD and 20 healthy controls were included in the study. Patients were examined using UPDRS, HADS, MoCA test. Expression of miR-185-5p, miR-29c-3p, miR-129-1-5p and miR-135b-5p has been measured in blood leukocytes. We performed total RNA extraction, then reverse transcription with stem-loop primers, followed by real-time PCR with fluorescent probes. Data analysis was performed with Statistica 10.0.



Results: miR-29c-3p showed a significant difference in the expression in PD (4,14±0,93) and control group (5,31625±1,35) (t-test, p=0,0006). There was no correlation with UPDRS, MoCA, HADS score, age or disease duration. No difference was found in expression of miR-185-5p, miR-129-1-5p and miR-135b-5p.
Conclusions: miR-29c-3p could be a promising biomarker in PD. Further investigations on a bigger amount of patients are needed.

P11
Parkinson's Disease diagnosis by recurrent neural networks on fMRI data

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Background: In this work, we designed and implemented a computational model based on recurrent neural networks (RNN) with resonate-and-fire neurons (RAF). With that model, we estimated neurobiological parameters using functional magnetic resonance imaging (fMRI) in Parkinson's disease (PD) patients and healthy controls (HC) to develop a prototype tool for the diagnosis of PD. We envision that such an approach will allow for a better understanding of PD and help doctors and centers design novel therapies.
Methods: We programmed the computational model and tested it with synthetic and real data. We used the synthetic data to assess the performance of the network. We used publicly available data from the Parkinson's progression markers initiative (PPMI) for training and classification purposes.
We downloaded the 20 PD patients with structural and functional MRI data and pairwise matched patients with HC by gender and age. We extracted time series from caudate-putamen regions and estimated the neuronal parameters at the subject level. Then, we compared the distribution of the parameters between PD patients and HC using statistics intending to find significant differences between groups.
Results: The novel model implementation shows a better performance compared to goal standard approaches, which use simple neuron models. When we applied this novel approach to neuroimaging data, the model estimated neurobiological parameters suggested better discrimination and generalization between PD and HC groups compared to state-of-the-art methods.
Conclusions: Performance evaluation indicates that the novel approach overcomes other existing methods in the literature. Moving forward, when we used the same models to interrogate neuroimaging data to discriminate between PD patients and HC, we obtained promising

results. While findings are yet preliminary, further improvement of this implementation can lead to a promising clinical tool that we can use to advise diagnostics and early detection of neurodegenerative disorders such as PD.

P12
Diffusion-weighted MRI as a tool to analyse the integrity of cholinergic tracts in subtypes of Parkinson's disease

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Background: To analyse the white matter integrity of the cholinergic-associated structure, the nucleus basalis of Meynert (NbM) in two subtypes of Parkinson's disease (PD), being the tremor-dominant (TD) and postural imbalance and gait disorder (PIGD) subtype, using diffusion-weighted MRI (dw-MRI).
Methods: Baseline data of the DUPARC study, a longitudinal *de novo* PD cohort, including dw-MRI and clinical motor assessment of 60 TD-PD and 48 PIGD-PD dopa-naive patients were analysed using a voxel-based analysis of white matter tracts associated with the nucleus basalis of Meynert (NbM). The means of FA and MD within these tracts were extracted for linear regression analyses. Age, sex, and the F-DOPA striatal-occipital ratios were included as covariates.

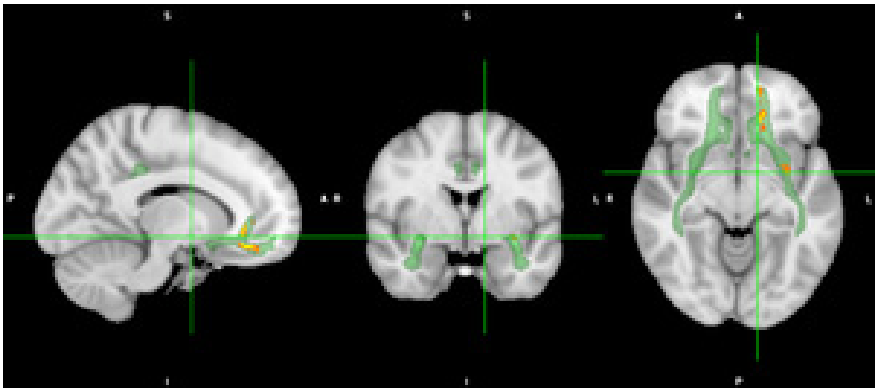

Figure. Voxel clusters with FA significant reduction in PIGD-PD compared to TD-PD (orange-yellow gradient) in the NbM-associated white matter pathway (green colour)

Results: The PIGD-PD group showed significantly lower FA vs. the TD-PD group (*P < 0.05,* family-wise error corrected, figure*)* at the proximal part of the lateral and medial pathways of the white matter tracts associated with the NbM, however only in the left hemisphere. Regression analyses showed that lower FA and higher MD within the NbM-related-white-matter tracts were associated with the severity of the axial and gait impairment [FA: b = -0.745 (–1.131, -0.359), *P* < 0.001; MD: b = 0.947 (0.532, 1.362), *P* < 0.001] but not to the total tremor severity.
Conclusions: The subtype of PIGD-PD is related to a left hemispheric loss of white matter tracts, associated with NbM-related projections, suggesting a lateralized cholinergic neuron loss.

P13
Analysis of brain structural connectivity networks and white matter integrity in patients with early Parkinson's disease: A longitudinal study

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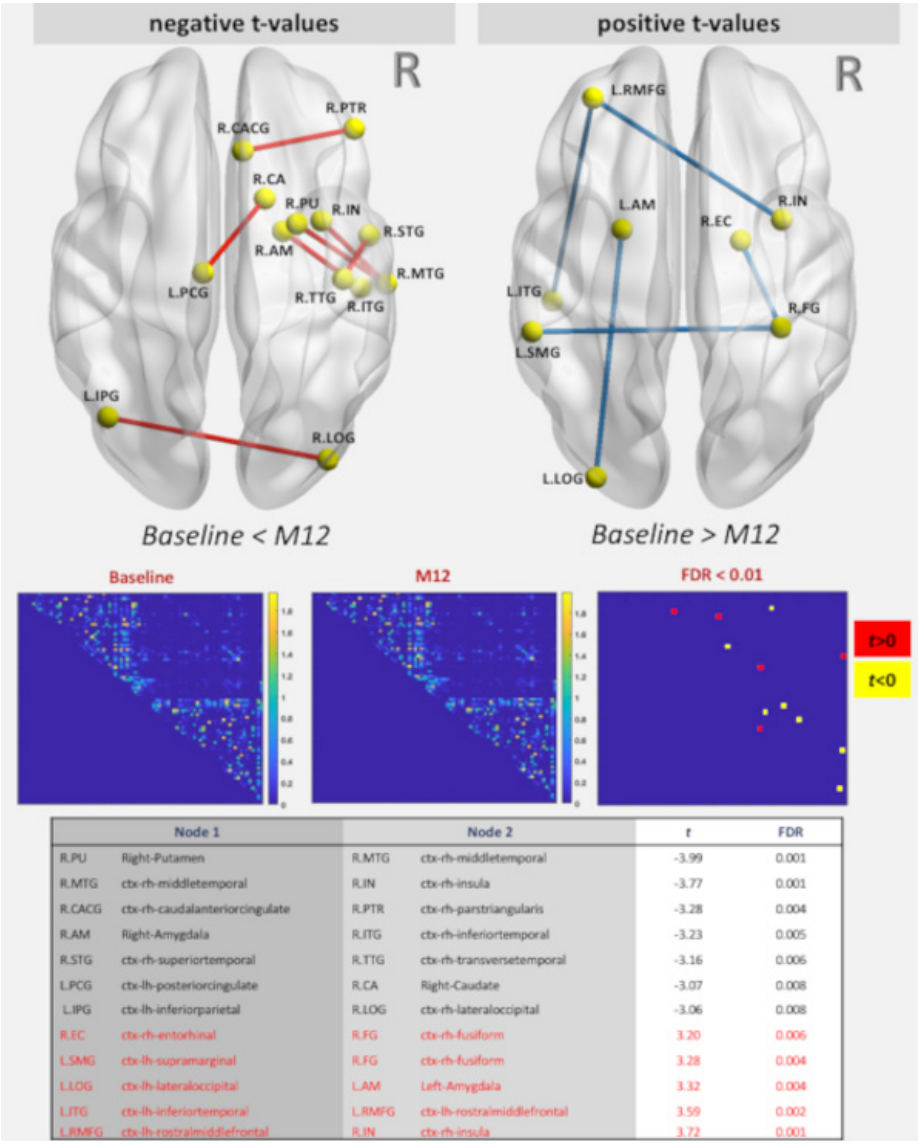
Background: Parkinson's disease (PD) is a neurodegenerative disease that leads to significant disability and morbidity. Here, we used DTI and a novel approach to analyze structural connectivity and WM integrity in people with early-PD over a 12-month follow-up (baseline and M12). Diffusion MRI data were downloaded from the PPMI database [https:/ida.loni.usc.edu/].
Methods: Thirty-five early-PD (baseline-age mean ± S.D. = 62 ± 10 years; 13 females) were included in this study. Pre-processing was performed by Mrtrix3, FSL, and ANTs. Tractography was performed with 5 million seeds using the iFOD2 algorithm. COMMIT2 algorithm was used to filter the connectivity matrices. A two-compartment Ball-and-Stick model was used to generate intracellular (IC) and isotropic (ISO) compartments.
Results: Compared with the baseline, higher values of FA and IC and lower values of ISO were found at M12. Connectometry analysis found differences between TPs in seven tracts with M12>baseline, and in other five tracts with M12<baseline (Figure 1).
Conclusions: We used DTI data to detect alterations in WM integrity and structural connectivity in early-PD. Other longitudinal studies have shown increased FA during follow-up. Our results using an advanced analytic approach demonstrates that elevated FA, IC, and structural connectivity in early-PD after 12 months may indicate true pathophysiological evolution in PD.



Node 1		Node 2		t	FDR
R.PU	Right-Putamen	R.MTG	ctx-rh-middletemporal	-3.99	0.001
R.MTG	ctx-rh-middletemporal	R.IN	ctx-rh-insula	-3.77	0.001
R.CACG	ctx-rh-caudalanteriorcingulate	R.PTR	ctx-rh-parstriangularis	-3.28	0.004
R.AM	Right-Amygdala	R.ITG	ctx-rh-inferiortemporal	-3.23	0.005
R.STG	ctx-rh-superiortemporal	R.TTG	ctx-rh-transversetemporal	-3.16	0.006
L.PCG	ctx-lh-posteriorcingulate	R.CA	Right-Caudate	-3.07	0.008
L.IPG	ctx-lh-inferiorparietal	R.LOG	ctx-rh-lateraloccipital	-3.06	0.008
R.EC	ctx-rh-entorhinal	R.FG	ctx-rh-fusiform	3.20	0.006
L.SMG	ctx-lh-supramarginal	R.FG	ctx-rh-fusiform	3.28	0.004
L.LOG	ctx-lh-lateraloccipital	L.AM	Left-Amygdala	3.32	0.004
L.ITG	ctx-lh-inferiortemporal	L.RMFG	ctx-lh-rostralmiddlefrontal	3.59	0.002
L.RMFG	ctx-lh-rostralmiddlefrontal	R.IN	ctx-rh-insula	3.72	0.001

Figure 1. Connectometry analysis detected differences in structural connectivity between baseline and M12. In the FDR matrix (bottom-right plot), the yellow points are the edges with negative t-values (baseline<M12), the red points are the edges with positive t-values (baseline>M12. The p-values are corrected for multiple comparison by FDR.

Neurosurgery (including Deep Brain Stimulation)

P14
First clinical and technical observations on a novel DBS implant capable of simultaneous chronic sensing and stimulation

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Background: A prerogative of new deep brain stimulation (DBS) devices is the capacity to record and process neural signals in order to regulate and tailor the stimulation delivery. Here we document the key advances and pitfalls of the Percept PC (Medtronic, PLC), one of the first commercially available devices capable of recording brain local field potentials (LFP) from chronically implanted leads, wirelessly and during stimulation.
Methods: We collected clinical and neurophysiological data of 14 patients with Parkinson's disease (PD) implanted in the subthalamic nucleus (STN), and five with dystonia implanted in the internal globus pallidus (GPi) who received the Percept PC.
Results: The Percept PC reliably recorded in all subjects continuous LFP signals from the implanted contacts. In PD, we identified a beta peak in 19/22 STN, along with movement- and medication-related modulations. We also leveraged the functionality that enables home recordings (one sample every 10 minutes up to two months) and assessed the possibility to track beta band changes aligned with circadian rhythms in three PD patients. In dystonic patients, we identified theta peak in all 8/8 GPi, but movement artefacts affected the reliability of these recordings. In two PD patients high power artefacts appeared in the gamma band at subharmonics (1/2, 1/4 or 3/4) of the stimulation frequency at high stimulation amplitudes. In up to 20% of our patients, the LFP recordings were also affected by cardiac artefacts.
Conclusions: The sensing capabilities of the Percept PC may help optimizing the efficacy of existing neuromodulation therapies and foster new knowledge. Such devices can help introducing brain sensing in clinical practice, whether to guide the selection of the optimal stimulation parameters or to identify novel biomarkers for closed-loop therapies.

P15
Effects of subthalamic and nigral costimulation on cortical network activity in freezing of gait in Parkinson's disease

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Background: Recently, freezing of gait (FOG) in Parkinson's disease (PD) has been linked to dysfunctional communication within the cortical-subcortical motor network. Due to its dense interconnection to mesencephalic and cortical areas, additional deep brain stimulation (DBS) of substantia nigra pars reticulata (SNr) beneath the subthalamic nucleus (STN) has emerged as a potential therapeutic strategy for PD patients suffering from freezing of gait (FOG).
The aim of this study was to investigate effects of STN+SNr-DBS on cortical motor network activity in gait execution to evaluate the underlying mechanisms of action of STN+SNr-DBS.
Methods: 21 age-matched healthy controls and 12 PD patients with frequent FOG and chronically implanted DBS electrodes within the STN/SNr were tested. Subjects performed a stepping-in-place task (SIP) in three different conditions in a randomized order: 1. STN-DBS 2.STN+SNr DBS 3. STIM OFF. Stepping symmetry and freezing episodes were detected using biomechanical sensors. Cortical activity was recorded using 64-channel-EEG. Power spectrum densities and functional coupling of defined cortical areas were analysed in terms of 1. effective stepping vs. freezing and 2. Different DBS conditions.
Results: We found that step asymmetry during SIP was significantly improved by STN-SNr DBS compared to STN- DBS ($t(11) = -3.0385$, $p = .013$) and STIM OFF ($t(11) = -2.372$, $p = .039$) while step asymmetry was correlated to FoG severity ($r_s = -.7853$, $p = .004$).
We currently investigate EEG functional connectivity within the cortical network during effective stepping and freezing episodes focusing on differences between STN-DBS and additional SNr stimulation.
Conclusions: So far, the present study demonstrates that combined STN+SNr DBS improves temporal SIP parameters directly affecting vulnerability to FoG. This study is designed to investigate neurophysiological effects of STN+SNr DBS on cortical network activity contributing to the understanding of the mechanisms of action of DBS effects on gait and freezing of gait.

P16
Clinical improvement at follow-up post-surgical patients by deep brain stimulation in Parkinson's disease: A retrospective cohort study

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Background: Parkinson's Disease (PD) dopamine treatment initially is highly effective. As the disease progresses, pharmacological tolerance occurs, demanding higher levodopa-equivalent-daily-dose (LEDD).

Deep Brain Stimulation (DBS) has been developed, focused in reducing medication-refractory symptoms. Studies described significant improvement in motor-domains. Quality of life (QoL) is not-well defined.

This study aims to describe and compare clinical characteristics between post-surgical subthalamic-nucleus patients (STN-DBS) and medical-treatment, with a 1-year follow-up.

Methods: A retrospective comparative cohort with a 1-year follow-up was conducted. The surgical-group includes STN-DBS patients and a medical-group matched by age, gender, and disease duration with a 2:1 ratio. MDS-UPDRS-III scale to evaluate clinical motor symptoms and, subcategorization based on rigidity, bradykinesia, tremor, and, gait and posture items was performed. NMSS was used to evaluate non-motor symptoms. QoL was evaluated with PDQ8-SI.

Results: A total of 75 subjects were included, surgical-group (25) and medical-group (50). Mean age was 51.3y (±7.5) with a mean PD duration of 8.2y (±3.5).

In comparative analysis, significant results were found in surgical-group in bradykinesia (8.5±6.2vs12.8±10.3, p=0.002) and LEDD (870±468vs641±282, p<0.01), since the baseline concerning the medical-group. Non-statistical differences were found in other domains.

At 1-year follow-up, the surgery-group had significant improvement on MDS-UPDRS-III (22±13.3vs32±16.4, p=0.012), rigidity (2±3.5vs4 ±5, p=0.047), and tremor (3±5vs6±6.25, p=0.006), concerning medical-group, which seemed to be equal at baseline. Non-difference was found in NMSS excepting urinary domain, with an improvement in the surgical-group (4.9±8.5vs7.3±8.3, p=0.034).

Conclusions: Surgical-group had an important improvement on MDS-UPDRS-III, especially in rigidity and tremor concerning medical-group baseline. Paradoxically, there is no difference in QoL at follow-up, however surgical-group trends to show better QoL scores, this result could probable being significant with a longer follow-up.

Therefore, it is necessary to carry out more studies with a larger sample and longer follow-up to confirm or rule out the aforementioned.

P17
Study of variability in power spectral density of beta band in STN

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Background: The local field potential (LFP) refers to the electric potential in the extracellular space around neurons. It is a summation signal of excitatory and inhibitory dendritic potentials from a large number of neurons in the surrounding regions of the recording site. LFPs has been subject of interest for marking the boundaries of STN specifically in PD patients.
Methods: Total of 8 PD patients, eligible for bilateral STN DBS as per CAPSIT-PD Protocol attending Department of Neurology, NIMS, Hyderabad, were included in the study after obtaining the consent. All patients underwent 3.0T MRI and planning for STN localization.
The surgeries were performed in the awake state. A Ben Gun approach was used for inserting 5 microelectrodes and macroelectrodes as well for final lead placement. Intra op recording of MUA and LFP on both the sides (left and right STN) was done, at 1 mm intervals from 5mm above to 5 mm below target. All microelectrodes were advanced simultaneously. Central electrode is separated from Anterior, Posterior, Medial and Lateral electrodes each by 2mm distance.
Recorded LFP data was analyzed offline using MATLAB. Data was down sampled and notch filtered for power line noise and its harmonics using notch filters. Beta band was obtained and its power spectral density was calculated.
Results: There was a significant difference in the PSD of beta band among the different anatomical regions. The beta power in STN was elevated in majority of the participants. Beta power in STN also varied considerably along its depth, being the strongest at the center.
Conclusions: Results from the current study indicate that the LFP can be used to mark different anatomical boundaries in PD patients undergoing DBS. It may also hold the key for identifying the target lead location more precisely based on the firing pattern in STN with the strongest power.

P18
Man in a barrel syndrome after deep brain stimulation procedure: A case report

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Background: Deep brain stimulation (DBS) is used to treat various refractory movement and psychiatric disorders through surgical implantation of electrodes into targeted areas of the brain. Although this procedure can lead to surgical complications, there are no known reports of DBS causing brachial diplegia, or Man in a Barrel Syndrome (MIBS), as a result of anoxic brain injury. This case demonstrates a novel complication of MIBS secondary to anoxic brain injury, to be wary of with DBS procedure.
Methods: Case Report.
Results: A 46-year-old male with refractory Parkinson's disease (PD) was admitted for pre-scheduled DBS implantation for severe dyskinesia of his lower extremities. During the procedure, after electrodes were advanced and sedation was weaned for the interactive portion, he developed decreased mentation, requiring intubation and abrupt discontinuation of the procedure. Workup revealed negative head CT and EEG. MRI brain ultimately revealed acute ischemia of bifrontal, biparietal, bitemporal and left occipital lobes, and right dentate nucleus, attributed to hypoxemia. His mentation improved but he was found to have new bilateral upper extremity plegia along with baseline PD-related lower extremity dyskinesias. He was admitted to inpatient rehabilitation where he progressed to minimum to maximum assistance for ambulation and activities of daily living (ADLs), with progression to minimum assistance level for ADLs and anti-gravity activation in bilateral upper extremities after two months of outpatient therapy.
Conclusions: MIBS involves bilateral upper extremity weakness with preserved head, neck and lower extremity strength. It is usually caused by impaired blood flow to the brain--specifically the watershed regions--as seen after cardiac arrest, severe vascular injury, head trauma, or poisoning. This case highlights an unusual etiology of anoxic brain injury and subsequent MIBS as a possible complication of DBS that physicians should be aware of when offering DBS for movement disorders.

Behavior, Cognition, Psychiatry

P19
Trait anxiety as a risk factor for impulse control disorders in Parkinson's Disease

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Background: Approximately 6-15.5% of patients with Parkinson's disease (PD) experience impulse control disorders (ICDs), characterized by a loss of voluntary control over impulses, drives, or temptations regarding excessive hedonic behavior.
The present study aimed to assess the role of anxiety and depression, and their interaction with dopaminergic medication types, in ICD development in *de novo* PD patients.
Methods: We selected 334 ICD-free *de novo* PD patients from the Parkinson's Progression Markers Initiative database (www.ppmi-info.org). ICD presence was assessed via the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP). Symptoms of anxiety and depression at baseline were measured via the State-Trait-Anxiety Inventory (STAI-Y) and Geriatric Depression Scale (GDS-15), respectively. Medication type was classified as dopamine agonists versus other dopaminergic medication types. Prospective ICD development was defined as a positive QUIP score during four-year follow-up.
Results: In total, 149 participants (44.6%) developed an ICD and the average onset time was 34.54 months (*SD*=24.74) from baseline. Results of a Cox proportional hazard model showed that higher baseline STAI-Y scores as well as dopamine agonist use were associated with increased risk of ICD development.
When further exploring anxiety, trait but not state scores caried an increased risk of ICD development. Importantly, these effects remained significant after controlling for age, gender, and UPDRS motor scores.
Conclusions: The finding that higher trait anxiety levels in *de novo* PD patients represent an ICD risk factor highlights the need for early anxiety screening in these patients.
Additionally, this risk may be elevated in patients receiving dopamine agonists. The present results may ultimately help clinicians and patients in making informed treatment decisions, by determining the extent to which a patient is at risk for ICD and balancing priorities regarding beneficial motor effects versus adverse impulsivity effects of dopaminergic treatments, reducing secondary consequences and increasing quality of life.

P20
The effect of COVID-19 related stressors on mental health in people living with Parkinson's disease

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Background: This study aims to investigate the impact of COVID-19 stressors on mental health in people living with Parkinson's disease.
Methods: This cross-sectional study uses baseline data of the PRIME Parkinson Evaluation Study. COVID-19 stressors were measured using an eight-item questionnaire. A total COVID-19 stressor score was calculated, as well as a social stressors and care stressors sub score. Depression was measured with the Beck Depression Inventory (BDI) and anxiety with the State-Trait Anxiety Inventory (STAI). Outcomes were standardized and adjusted linear regression models were fitted.
Results: A total of 822 participants with Parkinson's disease were included. The mean (SD) age of the participants was 70.2 (7.9) years and 311 (37.8%) were women. Figure 1 shows the associations between COVID-19 stressors and the BDI and STAI. The largest associations were observed for the stressor tension or conflict at home (beta BDI: 0.17, 95% CI: 0.10;0.24, beta STAI: 0.24, 95% CI: 0.17;0.30). The association between care stressors and BDI was higher in women (beta men: 0.04, 95% CI: 0.01;0.08, beta women: 0.11, 95% CI: 0.06;0.16) and the association between social stressors and STAI was higher in the higher education stratum (beta lower education: 0.01, 95% CI: -0.02;0.06, beta higher education: 0.08, 95% CI: 0.06;0.11).

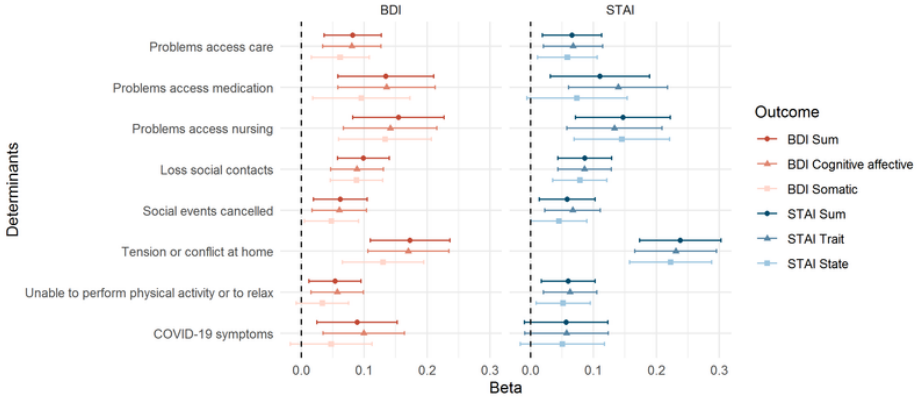

Figure 1

Conclusions: Our results suggest that a broad range of COVID-19 related stressors are affecting mental health in people living with Parkinson's disease. These effects are apparent across subgroups of people living with Parkinson's disease, most distinctly in women and highly educated persons.

P21
Non-motor correlates of subjective emotional experience in Parkinson's disease

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Background: Affective disorders in Parkinson's disease (PD) concern several components of emotion including subjective emotional experience. Most research on emotional experience in PD used unimodal stimuli to elicit emotions, whereas few studies involved ecological stimuli, yielding overall varying results. To the best of our knowledge, no previous work assessed the association between subjective feeling and autonomic symptoms in PD.
We aimed to evaluate the subjective emotional experience and its relationship with autonomic symptoms and other non-motor features in PD patients.
Methods: We used a battery of film excerpts to elicit Amusement, Anger, Disgust, Fear, Neutral state, Sadness, and Tenderness in 28 PD patients and 17 healthy controls. Self-report scores of emotion category, intensity, and valence were analyzed. We explored the association between clinical and emotion self-reported scores in the PD group and assessed patient clustering based on relevant features.
Results: Tenderness occurrence and intensity of Tenderness and Amusement were reduced in PD patients. Four patient clusters were identified according to distinctive affective, autonomic, cognitive, and sleep disturbances. The greatest impairment in emotional experience was associated with the highest urinary symptom prevalence and greater autonomic and cognitive dysfunction. We concluded that the subjective experience of complex emotions is impaired in PD.
Conclusions: Non-motor feature grouping suggests the existence of disease phenotypes profiled according to specific alterations of emotional experience, with potential clinical implications for the adoption of precision medicine in PD. Further research on larger sample sizes, combining subjective and physiological measures of emotion with additional clinical features is needed to extend our findings.

Parkinson Disease: Genetics

P22
Increased menopausal age decreases the risk of Parkinson's disease: A Mendelian randomization approach

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Background: Sex hormones may protect dopaminergic neurons, possibly preventing or delaying the onset of Parkinson's disease (PD). Studies of PD using age of menarche or menopause as indicators of lifelong female hormone exposure reported inconsistent findings, possibly due to difficulties in reporting these life events accurately.
Here, we employed Mendelian Randomization to assess the association between age at menopause and age at menarche with PD risk.
Methods: We performed MR-Egger analysis using external GWAS summary data from the UK biobank to assess the association between genetic variants and age of menopause and age of menarche, respectively. The association between genetic variants and PD was assessed using data from two population-based studies (PASIDA, Denmark, and PEG, USA) that enrolled 1,737 female subjects (825 cases (CA), 912 controls (CO), and 2,430 male subjects (1,218 CA, 1,212 CO) of European ancestry.

We adjusted for ancestry, study, and age at the interview. We included independent variants (linkage disequilibrium R-square < 0.1) and a P-value of $5x10^{-8}$, 79 SNPs for the age of menopause and 307 for the age at menarche.
Results: There was no indication for directional pleiotropic effects based on the MR intercept. For each year increase in age of menopause the risk for PD decreases (OR: 0.80, 95%CI: 0.64-0.99, P:0.04) among women with a natural menopause, while there was no association among men (OR: 1.03, 95%CI: 0.88-1.22, P:0.68).
In sensitivity analysis among various subgroups, using different subsets (P-value thresholds) and standard inverse variant weighting method for MR, the associations among women varied only slightly. There was no indication for an association between age at menarche and PD (OR: 1.34, 95%CI: 0.68-2.64, P:0.40).
Conclusions: A later age at menopause was associated with a decreased risk of PD in women, supporting the hypothesis that sex hormones may be neuroprotective in PD.

P23
Remote assessment of Parkinson's disease in a LRRK2 G2019S cohort

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Background: To compare self-reported Parkinson's disease (PD) diagnosis, remote clinical assessment, and remote application of diagnostic criteria in a national cohort of LRRK2 G2019S carriers with and without PD.
Methods: 23andMe-identified LRRK2 G2019S carriers (n=277) with and without PD enrolled in a 36-month decentralized, observational study and completed a baseline video-based visit. Participants completed patient-reported outcome measures assessing motor, psychiatric, and sleep domains. We collected medications, reviewed PD diagnostic testing, and completed a Montreal Cognitive Assessment (MoCA). A movement disorders specialist conducted a clinical assessment, including the modified Movement Disorder Society – Unified Parkinson Disease Rating Scale (MDS-UPDRS) motor examination and applied the National Institute of Health (NIH), Movement Disorder Society (MDS), and United Kingdom Brain Bank (UKBB) PD diagnostic criteria. Investigators were blinded to self-reported PD status.

Results: Altogether, 59 self-reported PD (mean (SD) age 68.6 (8.4), 53% female) and 215 self-reported no PD (mean (SD) age 54.1 (15.1), 59% female). Agreement between self-reported diagnosis and clinician assessment was high (kappa = 0.94, 95% CI 0.89-0.99). The clinician-determined PD cohort (n=59) had a mean (SD) modified MDS-UPDRS motor score 22.0 (10.8) and MoCA score 27.0 (2.2). Agreement between self-reported diagnosis and diagnostic criteria was moderate (kappa = 0.45, 95% CI 0.32-0.57) for the MDS criteria, moderate (kappa = 0.46, 95% CI 0.33-0.59) for the UKBB criteria, and good (kappa = 0.79, 95% CI 0.70-0.88) for the NIH criteria.

		MDS		UKBB		NIH		Expert-assessed	
		yes	no	yes	no	yes	no	yes	no
Self-reported PD	yes	20	38	22	36	45	11	59	0
	no	4	210	3	210	9	204	6	209

Table 1: Diagnostic Agreement

Conclusions: Self-reported PD status in this LRRK2 G2019S cohort is accurate. However, the use of diagnostic criteria developed for idiopathic PD in decentralized studies of genetic PD is not recommended.

P24
Enrichment of rare variants in E3 ubiquitin ligase genes in early onset Parkinson's disease

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Background: Dysfunction of ubiquitination proteasome system is important in the pathogenesis of Parkinson's disease (PD). Patients with early onset PD (EOPD) are more susceptible to genetic factors. We systematically examined the overlaps between E3 ubiquitin ligase genes and EOPD.
Methods: A total of 695 EOPD patients were sequenced with whole exome sequencing. Aggregate burden for rare variants (MAF <0.001 and MAF <0.0001) in a total of 44 E3 ubiquitin ligase genes causing disorders involved in the nervous system were analyzed.
Results: There was significant enrichment of the rare and rare damaging variants in the E3 ubiquitin ligase genes in EOPD patients. Detailly, in the gene-based level, the strongest associations were found in *HERC1, IRF2BPL, KMT2D, RAPSN, RLIM, RNF168* and *RNF216.*

Conclusions: Our findings highlight the importance of UPS mechanism in the pathogenesis of PD from the genetic perspective. Moreover, our study also expanded the susceptible gene spectrum for PD.

P25
Mitochondrial-derived peptide, SHLP2, as a potent protective factor in Parkinson's disease

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Background: Mitochondrial dysfunction has been shown to contribute to Parkinson's disease (PD) etiology and progression. Mitochondrial DNA (mtDNA) is highly polymorphic and mtDNA sequencing in large cohorts revealed that mtDNA polymorphisms could play a role in PD. Although such associations have been studied in population genetics, the functional effects of the mtDNA single nucleotide polymorphisms (mtSNPs) are underexplored. Our lab hypothesizes that mtDNA SNPs could affect MDPs, and we recently showed that a mtDNA SNP is associated with reduced circulating levels of an MDP called humanin and with cognitive decline. How other mtDNA SNPs affect MDPs and disease risk has yet to be analyzed.
Methods: We identified a mtSNP (m. 2158 T> C) in the region of the mitochondrial-derived peptide, SHLP2, that reduces the risk of PD. Of note, this SNP changes lysine (K) 4 to arginine (R) of a MDP called SHLP2, which is encoded by the 16S rRNA region of the mtDNA. SHLP2 acts as a neuroprotective factor and as a metabolic regulator. We treated neuronal cells and MPTP mice with SHLP2 and its variant and examined protection against mitochondrial dysfunction and neuronal cell death.
Results: The SHLP2 SNP leads to amino acid substitution in SHLP2 and produces a K4R-SHLP2 variant. K4R-SHLP2 has higher stability compared to WT and superior protection in PD toxin-based neuronal cells and TFAM$^{+/-}$ MEFs. K4R SHLP2 prevents dopamine depletion in MPTP injected mice model of PD. We also found that plasma SHLP2 levels are elevated in PD patients early in the disease but are inversely correlated with PD-related cognitive decline later on. We also found that SHLP2 gene expression is upregulated in the prefrontal cortex of postmortem brains from PD patients.
Conclusions: Altogether, SHLP2 has the therapeutic potential as a precision medicine in PD.

P26
GBA screening in Nigerian patients with Parkinson's disease

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Background: Heterozygous mutations in the glucocerebrosidase (GBA) gene are a major genetic risk factor for PD and there few genetic studies performed in people with PD from Sub-Saharan African. The aim of the study was to screen the GBA gene in Nigerian patients with PD and healthy controls.

Methods: We screened 92 Nigerian PD patients and 52 controls with a nested (to avoid pseudogene contamination) PCR-Sanger sequencing approach for all 11 exons. The potential pathogenicity of revealed variants was checked with CADD score, PolyPhen-2, SIFT and ClinVar softwares.

Results: In the study group, mean (SD) the age of onset was 60.0 (9.1) years, and 64 participants (69.6%) were men. The age at study was 63.3 (9.2) in PD patients and in the control group, mean (SD) age was 64.4 (8.9) years, and 37 participants (72.5%) were men. There were 10 variants (5 missense, 4 synonymous and 1 loss of function) in PD group and 4 in controls (3 missense and 1 intronic). The mutations predicted as pathogenic were only identified in 6 (6.5%) PD patients (W223R n=1, L422PfsX3 n=2 and L483P n=3).

Conclusions: Heterozygous GBA mutations are present in Nigerian patients with PD, although no individual variant was considered common. Further genetic studies are needed in sub-Saharan Africa.

P27
Mutation analysis of seven *SLC* family transporters for early-onset Parkinson's Disease in Chinese population

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Background: The *solute carrier* (*SLC*) transporters have been suggested to play important roles in neurodegenerative disorders. Recently, seven *SLC* transporters were identified to be associated with Parkinson's disease (PD) by genome-wide association studies. However, few replications were conducted, and whether rare variants in these genes were associated with PD was not explored yet.
Methods: To elucidate the genetic associations of these *SLCs* with PD, we investigated the rare variants in 743 Chinese early-onset PD (EOPD) patients using whole-exome sequencing, and evaluated the association between rare variants and PD at allele and gene levels.
Results: Totally, 58 rare variants were identified in *SLC50A1*, *SLC41A1*, *SLC45A3*, *SLC44A4*, *SLC56A2*, *SLC2A13* and *SLC38A1*. At allele level, six variants were nominally associated with PD, namely p.S423G in *SLC45A3*, p.I551V, p.T435S, p.R323C and p.V101M in *SLC2A13*, and p.R285Q in *SLC41A1*. Gene-based burden analysis showed enrichment of rare variants of *SLC2A13* in EOPD.
Conclusions: Our study systematically analyzed the genetic involvement of *SLCs* in EOPD, identified *SLC2A13* as a risk gene for PD, and broadened current mutation spectrum of PD.

P28
α-synuclein injuries the dopaminergic neurons by regulating KLF9 expression via long non-coding RNA regulatory network

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Background: Accumulating evidence have presented the pathologic α-Synuclein transferring between the cells as an important mechanism in the progression of Parkinson's disease. In this study, we aimed to explore how α-synuclein injuries the dopaminergic neurons by promoting cellular oxidative stress.

Methods: The experiments were carried out upon the cellular model induced by α-Syn and pathologic α-Syn stereotactic injection mice. The expression of T199678 and KLF9 was detected by qPCR or Western blot. The location of T199678 in vitro model and KLF9 in vivo was observed via Fish technique and immunohistochemical staining.
Lastly, we used the flow cytometry to determined the cell growth cycle change, and use the DCFH-DA assay to detect the ROS content in cells.
Results: According to the data, we found the pathologic α-Syn could up-regulate the expression of KLF9 in the SH-SY5Y cells as well as the dopaminergic neurons of mice. What's more, the in vitro experiment indicated that the down-regulation of T199678 might result in the overexpression of KLF9 and the enhance of ROS content and the disturbance of life cycle.
Conclusions: So we supposed that exogenous α-Syn would lead to the oxidative stress in dopaminergic neurons by regulate the expression of T199678 and KLF9. This investigation would help to seek new pathogenesis hypothesis and research target of the neurodegenerative pathological change.

P29
Association of SNCA (E46K, A53T, A30P) gene polymorphisms and their correlation with CSF α- Synuclein in PD patients

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Background: Mutations in SNCA causes autosomal-recessive PD by self-aggregation and oligomerization into protofibrils, compared with native-protein. 39 SNPs in SNCA-gene were found which increases PD risk.
Hence, the current study was designed to find association of SNCA (rs104893875, rs104893877, rs104893878) gene polymorphisms with PD risk and to correlate the CSF α- Synuclein in PD patients.
Methods: A total of 348 cases and 280 controls were recruited. DNA was isolated and polymorphisms were analyzed by PCR-RFLP method and validated by Sanger's sequencing. The CSF α- Synuclein was analyzed using luminex multiplex platform.
Results: Mean age of cases and controls was 57.04±0.57 yrs and 56.12±0.71 yrs. The mean age at onset was 50.52±0.60 yrs and disease-duration was 6.86±0.22 yrs. The mean UPDRS III OFF, ON scores was 52.77±0.63; 15.23±0.35. The mean change in aLR was 37.48±0.50, the disease-severity was 2.65±0.04 and MoCA was 27.64±0.14. The mean S&E-score was 67.92±0.84 and PDQ39-score was 62.48±1.58.

Only wild genotypes were present, heterozygous and mutant genotypes were absent in rs104893875, rs104893877 polymorphisms whereas, rs104893878 heterozygous genotype was found to be significantly more common among controls whereas homozygous mutant genotypes were absent.
Significantly reduced CSF α-Synuclein levels were found (2246±285.2 pg/ml, p=0.007) compared to healthy controls (4381±735.7 pg/ml). Tetraplot software used to draw the contour plot considering CSF DJ1, α-synuclein, disease severity in X, Y and Z-axes, respectively. α-synuclein was found to have synergistic association (no independent effect). Lower levels of α-synuclein were associated with higher disease severity. CSF α–Synuclein was not correlated with polymorphisms as mutants were not found.
Conclusions: SNCA E46K, A53T, A30P gene polymorphisms were not associated with PD in south Indian population. CSF α–Synuclein levels significantly reduced in cases and could be considered to be a biomarker with 65% specificity and 52% sensitivity.

Parkinson Disease: Subtypes, natural course

P30
Apathetic PD patients have more dopamine-resistant motor symptoms

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Background: We have investigated the association between specific motor symptoms and presence of apathy in Parkinson's disease (PD).
Methods: We recruited 76 patients through our outpatient clinic and screened for apathy using the Lille Apathy Rating Scale (LARS). Patients with a LARS score higher than -21 were considered apathetic. We defined three categories: mildly (-21 to -17), moderately (-16 to -10) and severely (-9 and above) apathetic. Motor symptoms were evaluated using the Movement Disorders Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Using the UPDRS-III, we formed clusters that reflect specific PD symptoms: Speech, Facial, Rigidity, Akinesia, Axial and Tremor.
Results: In our sample, 56 patients (74%) were male. Mean age was 67.8 (10.2) and mean disease duration 7.7 (5.4) years. Of our sample, 46 (60.5%) were apathetic. Of these 46 patients, 22 (47.8%) had mild, 13 (28.2%) moderate and 11 (23.9%) severe apathy. Apathy subgroups were different in terms of disease duration (p=0,02) and total UPDRS-III score (p=0,01). When comparing symptom clusters, we found a significant difference in scores of *Speech* (p=0,03), *Bradykinesia* (p=0,01) and *Axial* (p=0,018) between apathy groups. Mean motor cluster scores correspond to severity of apathy, with the highest scores noted in the 'severe apathy' group. Other scores did not differ significantly. Interestingly enough, there was no difference in age between apathy groups.
Conclusions: It's known that apathetic PD patients have worse motor impairment however we found evidence that their motor manifestations are significantly different from non-apathetic patients. Apathetic patients are more likely to suffer from speech impediment, brady- and hypokinesia as well as axial symptoms. Apathy presents as a prodromal sign in some patients and might signal a less dopamine responsive phenotype in PD patients. Clearly there is need to elucidate this fascinating relationship as this non-motor symptom might even guide future therapeutic choices.

P31
Depression is the only determinant of self-stigma in Parkinson's Disease: A 3-year cohort study

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Background: We conducted a 3-year prospective longitudinal study to observe the development and evolution of self-stigma in patients with early-stage Parkinson's disease (PD) and to explore the associated and predictive factors of self-stigma in PD.
Methods: A total of 224 patients with early-stage PD (disease duration <3 years) were enrolled at baseline and followed up annually for three consecutive years. Self-stigma was assessed by the stigma subscale of the Parkinson's Disease Questionnaire (item 23-26). The generalized estimating equations model was applied to investigate the associated factors of self-stigma over 3 years, and the binary logistic model was used to explore the predictors of self-stigma in PD patients without self-stigma at baseline.
Results: The frequency of self-stigma in PD decreased from 58.1% at baseline to 52.6% after 3 years. The Hamilton Depression Rating Scale (HDRS) score was the only associated factor (B 0.160 [1.106-0.214], $P < 0.001$) of self-stigma over 3 years and the only predictor (OR 1.252 [1.044-1.502], $P = 0.015$) of the onset of self-stigma.
Conclusions: Self-stigma is very common in PD, but its frequency tends to decrease as the disease progression. Depression was the only associated and predictive factor of self-stigma in PD and could be an effective target of improving self-stigma.

P32
Prevalence of minor and major hallucinations in an online cohort of individuals with and without Parkinson's disease

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Background: To examine the prevalence of minor and major hallucinations in the Fox Insight cohort, a large, community-based online cohort of individuals with and without Parkinson's disease (PD).

Methods: Participants were asked to complete a novel, self-administered survey to identify the presence of minor and major hallucinations over the preceding month. Chi square tests were used to compare prevalence in PD versus control participants.

Results: A total of 47,640 individuals (34,572 with PD and 13,068 controls) were invited to participate. Of these, 4,211 (8.8%) completed the survey: 3,324 with PD (mean age 68.2±8.6 years; 52.6% male) and 887 controls (mean age 62.5±12.7 years; 21.2% male).

Minor hallucinations were significantly more prevalent in PD versus controls (45.1% vs 33.6%, $p < 0.001$). This included a higher prevalence of illusions (14.6% vs 8.5%, $p < 0.001$), passage phenomena (39.7% vs 29.2%, $p < 0.001$), and feeling of presence (10.4% vs 6.1%, $p < 0.001$) in PD versus controls.

Major hallucinations (25.5% vs 20.2%, $p < 0.001$), including visual (4.6% vs 1.4%, $p < 0.001$) and auditory hallucinations (8.5% vs 4.4%, $p < 0.001$) were significantly more prevalent in PD versus controls.

There were no differences in the prevalence of gustatory, olfactory, or tactile hallucinations between the two groups. PD participants were significantly more likely to report more than one type of minor hallucination (15.9% vs 8.8%, $p < 0.001$) or a combination of minor and major hallucinations (18.7% vs 11.6%, $p < 0.001$) versus controls.

Conclusions: Minor hallucinations are common in PD and controls, but are significantly more common and more often co-morbid with major hallucinations in PD. More work is needed to evaluate the features of self-reported "minor hallucinations" in healthy controls, validate the survey, and determine whether minor hallucinations in PD are associated with specific disease phenotypes or long-term outcomes.

P33
Progression of non-motor symptoms in early Parkinson's disease: A 3-year prospective cohort study

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Background: Little is known about the early dynamic trajectory of non-motor symptoms (NMS) in patients with Parkinson's disease (PD). This study aimed to examine the longitudinal evolution of NMS in patients with early-stage PD who finished a 3-year prospective follow-up.
Methods: A total of 224 patients with early PD who underwent annual evaluation using repeated measurements of the Non-Motor Symptoms Scale (NMSS) were included. The Generalized linear equation (GEE) model was used to determine the factors associated with the number of NMS. Significant longitudinal outcome changes in NMSS score were analyzed with the Friedman test. The forward binary logistic regression models were used to determine the association between the number of NMS at baseline and motor progression in PD.
Results: Most NMS in the NMSS increased from baseline to 3-year except for sexual dysfunctions and mood/apathy. Significant deteriorations were observed in the sleep/fatigue, perceptual problems/hallucinations, attention/memory, gastrointestinal, urinary, and miscellaneous domains ($P<0.05$).
The number and score of sexual dysfunctions were decreased. All NMSS domains showed a small effect size from baseline to 1-, 2-, and 3-year follow-up (effect size <0.5). The total number of NMS was significantly associated with age (B 1.112, $P=0.001$) and Unified Parkinson's disease Rating Scale (UPDRS) III score (B 1.124, $P<0.001$). A high number of NMS at baseline was associated with the UPDRS III 3-point increase from baseline to 1-year (odds ratio [OR] 1.074, $P=0.017$), 6-point increase from baseline to 2-year (OR 1.113, $P=0.001$), and 9-point increase from baseline to 3-year (OR 1.117, $P<0.001$).
Conclusions: This study provides evidence that NMS evolution is slight and multidimensional in early PD. High NMS burden in the early stage of the disease accelerates the faster motor progression of PD.

Parkinson Disease: Clinical assessment (including devices)

P34
Trsper: A web-based application for archimedes spiral analysis

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Background: The Archimedes spiral exam is invaluable for diagnosis of movement disorders. Prior attempts to digitize the exam have used specific platforms (e.g. Wacom tablets). We built a web-based application of the Archimedes spiral exam that implements clinically validated spiral metrics and all touchscreen devices, available at: http://www.trsper.com.
Methods: We hosted an HTML5 and Javascript implementation of the spiral exam, which can run on most mobile touchscreen devices. Our application calculates 11 previously published metrics (e.g. first order smoothness) and performs a custom analysis to provide clinical decision support. We recruited 10 volunteers each for 2 experiments designed to validate the programmed spiral metrics and assess how instructions or drawing implement affect the results.
In task one, volunteers drew 5 spirals each while following 6 different instruction sets (n=30 spirals each, n=300 spirals total) that varied by contact of the drawing hand with the drawing surface and tracing condition (either tracing a spiral template, drawing in-between it, or freehand).
In task two, volunteers drew 5 spirals each while following 2 instruction sets and drawing using a stylus or their dominant index finger (n=20 spirals each, n=200 spirals total). We then used principal components analysis of multiple parameters and a custom distance metric to quantify both inter-instructional and inter-individual consistency in spiral drawing.
Results: Principal components analysis of 11 calculated metrics reveals that the experiments grouped by instruction set and by subject. Mean Euclidean distance between experiments represented as 11-dimensional vectors revealed that consistency varied among instruction tasks and that drawing with a stylus produced more consistent results than did drawing with the dominant index finger.
Conclusions: We built and validated a robust digital implementation of the Archimedes spiral exam and recommend a sensitive and specific workflow on the basis of data gathered from healthy volunteers.

P35
Efficacy of Opicapone at different Levodopa regimens up to a threshold of 600mg/day Levodopa in Parkinson's disease patients with motor fluctuations

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Background: Opicapone is a once-daily catechol-O-methyltransferase inhibitor approved as adjunctive treatment to levodopa/DDCI (dopa decarboxylase inhibitor) in Parkinson's disease (PD) patients experiencing OFF episodes. This *post hoc* analysis evaluated efficacy of opicapone in PD patients with motor fluctuations and receiving different levodopa regimens up to 600mg/day (mean total daily dose).

Methods: Matching efficacy data from the BIPARK-1 and BIPARK-2 studies were combined for the placebo and opicapone 50mg groups (studies had similar designs, eligibility criteria, and methodologies). Primary efficacy endpoint was change in OFF-time from baseline according to patient diaries.

Subgroup analyses were performed to evaluate the efficacy of opicapone 50mg in different daily levodopa regimens (300-400, 400-500 and 500-600mg/day).

Results: A total of 239/517 patients received levodopa 300-600mg/day (placebo, n=118; opicapone 50mg, n=121). Mean number (±standard error) of levodopa daily intakes by dose group was as follows: 300-400mg/day (placebo and opicapone, both 3.7±0.1); 400-500mg/day (placebo=4.3±0.1, opicapone= 4.4±0.1); and 500-600mg/day (placebo=4.5±0.1, opicapone= 4.3±0.1). Mean OFF-time reduction with opicapone 50mg added to any levodopa regimen was at least double that of placebo.

Mean changes from baseline in OFF-time for opicapone 50mg versus placebo by levodopa dose groups were as follows: 300-400mg/day (-102.2min [95% CI: -138.1, -66.3] versus -53.4min [-89.6, -17.3]); 400-500mg/day (-110.0min [-146.7, -73.3] versus -37.2min [-77.7, 3.3]); and 500-600mg/day (-117.6min [-152.6, -82.6] versus -23.1min [-67.8, 21.6]).

With increasing levodopa dose regimens, there was a trend towards decreasing magnitude of effect in the placebo group, compared with a trend towards a slight increase in magnitude of effect in the opicapone 50mg group.

Conclusions: In this subgroup analysis of combined BIPARK-1 and BIPARK-2 data, opicapone 50mg showed a similar magnitude of effect at several different levodopa dosing regimens, resulting in at least double the OFF-time reduction compared with placebo.

P36
Evaluation of changing clinical outcomes and disease burden in advanced Parkinson's Disease patients with different treatment patterns: PROSPECT Study

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Background: There is limited prospective real-world data describing the long-term changes in clinical outcomes and disease burden for individual advanced PD patients. The understanding of the treatment patterns and their differential impact over time is also limited.
Here we describe the changing clinical outcomes and disease burden of advancing Parkinson's disease in patients with motor fluctuations no longer controlled by current PD medications.
Methods: PROSPECT is a 24-month, prospective, observational study of advanced PD patients (>30 years of age) no longer adequately controlled by their current therapy and have a minimum of 2.5 hours of "Off" time per day. Study assessments will be performed at baseline (ie, study enrollment) and 4 follow-up visits at months 6, 12, 18, and 24.
Assessments will include the current treatment regimen, severity of disease (H&Y stage), changes in motor ("Off" and dyskinesia time) and non-motor symptoms (NMS scale and PD Sleep Scale-2), activities of daily living (UPDRS II), quality of life (PD Questionnaire-39 and EQ-5D), cognitive function (Mini-Mental State Evaluation), health care resource utilization, caregiver burden (Modified Caregiver Strain Index), treatment satisfaction and patient global impression of change in severity (PGIC-S). Comparative assessments between patients with different treatment patterns will occur at baseline to month 12 and month 24.
Results: This study will enroll approximately 550 advanced PD patients from an estimated 90 multinational sites.
Conclusions: This study will describe real-world long-term prospective insights on the natural progression of disease burden, clinical outcomes, and potential value of timely initiation of advanced therapies among patients with advanced PD.

P37
^{123}I-MIBG cardiac scintigraphy reflects disease burden, regardless of blood pressure instability, in Parkinson's disease

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Background: Cardiovascular dysautonomia is an early finding of Parkinson's disease (PD). Reduced uptake of ^{123}I-*meta*-iodobenzylguanidine (MIBG) cardiac scintigraphy and orthostatic hypotension (OH) are independently associated with worse clinical outcomes, and both are strongly associated. However, their interactive influence on PD have not been studied. The role of MIBG scan, as a biomarker of PD severity, was investigated, conditional on the mediating effects of OH.
Methods: Two hundreds twenty-seven newly diagnosed PD patients were enrolled. Their motor and non-motor aspects were assessed by Unified Parkinson's Disease Rating Scale Part II and III, Non-Motor Symptoms Scale, Montgomery-Asberg Depression, Epworth Sleepiness Scale, Parkinson's Disease Sleep Scale-, REM Sleep Behavior Disorder Screening Questionnaire, Orthostatic Hypotension Questionnaire, and Scale for Outcomes in Parkinson's Disease-Autonomic. Global disease burden (global composite score) was estimated by averaging the scaled z-scores of the assessment tools. Every patient went through ^{123}I-MIBG scan, and OH was evaluated by head up tilt test. The mediating role of orthostatic blood pressure changes (BP) on the association between cardiac sympathetic denervation and disease burden was investigated.
Results: The disease duration was 1.1 ± 1.0 years, and the total UPDRS score was 23.4 ± 11.9. 69.6% (158/227) had abnormal MIBG scan, and 22.9% (52/227) had OH. PD with abnormal MIBG was associated with OH, and they had worse disease burden than PD with normal MIBG (global composite score, z: normal MIBG *vs.* abnormal MIBG; -0.3 ± 0.5 *vs.* 0.1 ± 0.7; p<.001). The mediation model, controlled with age and disease duration, revealed that the negative association between delayed H/M ratio and global composite score was maintained within the context of non-mediating effects of orthostatic BP.
Conclusions: Adverse relationship between cardiac sympathetic denervation and disease burden was sustained without interference of orthostatic BP fluctuations. This result suggested that extracranial cardiac marker might reflect PD disease burden, regardless of labile BP influence.

P38
CLE-600: Treating nocturnal and early morning OFF symptomology in Parkinson's disease with the OLAR® platform

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Background: Levodopa Parkinson's disease (PD) treatment is limited by its short duration of effect and fluctuations in blood concentrations. Early wearing off during nighttime results in often-troublesome nocturnal symptoms and early morning OFF (EMO), particularly in patients with the onset of motor fluctuations. CLE-600 is being developed as a night pill for the treatment of PD nocturnal symptoms and EMO using a proprietary Oral Long Acting Release (OLAR®) drug delivery platform (see https://www.clexio.com/forpeople/#pipeline).
CLE-600 is designed to achieve stable and prolonged levels of Levodopa/carbidopa (LD/CD) above night therapeutic levels for 8-10hr, to enable Parkinson patient's symptomatic control during the night and into the early morning.
Methods: 18 healthy volunteers received Sinemet® 100/25 mg (LD/CD) tablet serving as the reference group for CLE-600. After a washout period of at least 48 hours, the subjects were administered CLE-600. Blood samples were collected at different time points between pre-dose and 24 hours post administration and assayed for plasma levodopa concentration. Subjects were also examined by fluoroscopy for the detection and location of the OLAR®.
Results: Following CLE-600 administration, stable LD levels were detected for more than 8hrs. Radiographic examination revealed that each OLAR® was fully open in the stomach within 10 minutes of administration and still present in the stomach at least 8 hours later. The administration of CLE-600 was safe and well tolerated, and a prolonged pharmacokinetic Levodopa profile was achieved.
Conclusions: The ability to treat PD night symptomology and early morning OFF, is a high unmet need in Parkinson's disease and among the main reasons for low Quality of Life (QoL) reported by PD patients. CLE-600 is being developed as the first oral solution dedicated for PD nocturnal problems and morning akinesia. CLE-600 results warrant further development and testing in Parkinson's patients experiencing nocturnal symptoms and EMO.

P39
Photobiomodulation modulates the microbiome and improves symptoms of idiopathic Parkinson's Disease: Results from a proof-of-concept trial

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Background: Increasing incidence of Parkinson's disease (PD) has significant health and economic consequences, which COVID-19 has exacerbated. There is need for improved therapies to address PD progression, symptoms, and quality-of-life. Photobiomodulation therapy (PBMt) utilising non-thermal, narrow-wavelength light is one such possibility. In this study, we assessed the safety and efficacy of PBMt on PD patients.
Methods: Effects of PBMt were investigated in phase-II-equivalent, multicentre proof-of-concept trials. Participants received intervention immediately or on a 12-week waitlist before intervention. PBMt was applied to the head, nose, cervical spine, and abdomen over 12-weeks on a regressive-frequency schedule (3-times/week for 4-weeks; 2-times/week for 4-weeks; 1-times/week for 4-weeks). A second study treated the abdomen and cervical spine only. Participants continued self-administered treatment for up to 1-year. Outcome measures included gait (timed-up-and-go, 10-metre walk), fine-motor control (9-hole peg test. micrography, spiral test), balance (step-test, tandem stance, single-leg stance), cognition (MoCA), sleeping patterns, and smell. Adverse indications were monitored throughout the study. Gut microbiome (GM) was analysed using participant faecal samples. Outcome measures were assessed before intervention, 12-weeks and 1-year post-intervention. Those on the waitlist were additionally assessed 12-weeks before intervention and after 4-weeks of intervention.
Results: Gait, balance and cognition were improved ($p<0.05$). Some participants showed non-statistical improvements in smell and sleeping patterns. These were sustained over 12-months. PBMt decreased PD-associated dysbiosis, and helped restore healthier GM profiles. A Hawthorne effect was observed in the waitlist participants. No adverse effects from PBMt were observed.
Conclusions: PBMt may provide sustained improvements (1-year) in PD clinical signs, with no adverse effects. PBMt can change GM in favour of more healthy profiles. PBMt has the potential as a non-invasive treatment option to slow/halt the progression of PD symptoms. Furthermore, recent evidence supports the gut/brain-origin PD model supporting the use of multiple treatment targets. Further larger RCTs are required to confirm these observations.

P40
Validation of the Korean version of the composite autonomic symptom scale 31 in patients with Parkinson's Disease

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Background: The composite autonomic symptom scale-31 (COMPASS-31) is a self-rated questionnaire that evaluates diverse autonomic symptoms.
In the present study, we developed the Korean version of COMPASS-31 with appropriate translation, and verified its reliability, and internal and external validity in patients with Parkinson's disease (PD).
Methods: The original version COMPASS-31 was translated independently into Korean by two bilingual neurologists. Test-retest reliability was evaluated with a 2-week time interval. We investigated the correlations between COMPASS-31, the scale for outcomes in PD-autonomic (SCOPA-AUT), and results of an autonomic function test (AFT), respectively.
Results: A total of 90 patients with PD (47 females; mean age, 63.4 ± 10.8 years) were enrolled. K-COMPASS-31 showed excellent test-retest reliability (intra-class correlation coefficient = 0.874, $p < 0.001$) and internal validity (Cronbach's α-coefficient = 0.878). The COMPASS-31 was positively correlated with SCOPA-AUT ($r = 0.719$, $p < 0.001$) and the results of the AFT.
Conclusions: In conclusion, K-COMPASS-31 showed excellent reliability and validity for the assessment of autonomic symptoms in PD patients. COMPASS-31 is an easy to repeat and widely used tool to investigate autonomic dysfunction in various neurologic disorders, therefore it allows comparison of autonomic dysfunction among neurologic disorders.
We recommend the K-COMPASS-31 as a valid instrument for use in clinical practice for patients with PD.

	Enrolled patients with PD N = 90
Female, n (%)	47 (52.2)
Age, years (SD)	63.4 (10.8)
Disease duration, years (SD)	4.2 (4.2)
UPDRS part III, (SD)	19.6 (11.3)
H & Y scale, (SD)	1.8 (0.8)
Levodopa equivalent daily dose, mg (SD)	417.7 (346.9)
MMSE, (SD)	27.3 (2.1)
Autonomic function profile	
SCOPA-AUT, (SD)	16.4 (11.2)
E:I ratio, (IQR)	1.11 (1.07 - 1.18)
Valsalva ratio, (IQR)	1.35 (1.18 - 1.53)
Pressure recovery time, sec (IQR)	1.7 (1.0 - 4.7)
Abnormality in SSR, n (%)	13 (14.4)

Table 1. Demographic data and results of autonomic function tests of enrolled patients with Parkinson's disease

PD - Parkinson's disease; SD - Standard deviation; IQR - Interquartile range; UPDRS - Unified Parkinson's disease rating scale; H & Y - Modified Hoehn and Yahr; COMPASS - Composite autonomic symptom score; MMSE - Mini-mental status exam; SCOPA-AUT - Scale for outcomes in Parkinson's disease-autonomic

K-COMPASS-31 domains	Mean (SD)	Median (range)
Total score, (SD)	22.0 (17.4)	17.4 (0-75.8)
Orthostatic intolerance, (SD)	9.7 (11.3)	4.0 (0-36.0)
Vasomotor, (SD)	0.3 (0.9)	0 (0-4.2)
Secretomotor, (SD)	4.5 (3.6)	4.3 (0-15.0)
Gastrointestinal, (SD)	5.0 (3.4)	4.9 (0-13.4)
Bladder, (SD)	1.8 (2.1)	1.1 (0-10.0)
Pupillomotor, (SD)	0.7 (1.0)	0 (0-5.0)

Table 2. Total and each domain scores of K-COMPASS-31

K-COMPASS-31 - Korean version of composite autonomic symptom score-31;
SD - standard deviation

K-COMPASS-31 domains	Age*	Disease duration*	SCOPA-AUT‡	AFT			UPDRS part III					H & Y‡	MMSE†	LEDD‡	NMSS§	PDQ-39-SI§
				E:I ratio‡	Total‡	Axial‡	Tremor‡	Rigidity‡	Bradykinesia‡	Valsalva ratio‡	PRT‡					
Total score	0.002	0.371ǁ	0.719ǁ	-0.321ǁ	0.204	0.333ǁ	-0.090	0.141	0.176	-0.343ǁ	0.338ǁ	0.186	0.087	0.336ǁ	0.442ǁ	0.430ǁ
Orthostatic intolerance	0.041	0.276ǁ	0.592ǁ	-0.198	0.120	0.221ǁ	-0.077	0.072	0.144	-0.302ǁ	0.293ǁ	0.133	-0.086	0.293ǁ	0.378ǁ	0.370ǁ
Vasomotor	0.045	0.265ǁ	0.303ǁ	-0.212ǁ	0.085	0.076	0.031	0.086	0.116	-0.309ǁ	0.187	-0.006	-0.047	0.219ǁ	0.213ǁ	0.176
Secretomotor	-0.050	0.342ǁ	0.493ǁ	-0.296ǁ	0.389ǁ	0.418ǁ	-0.011	0.363ǁ	0.330ǁ	-0.287ǁ	0.214ǁ	0.345ǁ	-0.055	0.165	0.347ǁ	0.308ǁ
Gastrointestinal	-0.138	0.215ǁ	0.562ǁ	-0.341ǁ	0.096	0.240ǁ	-0.034	0.025	0.289	-0.266ǁ	0.263ǁ	0.051	-0.132	0.207	0.195	0.192
Bladder	0.023	0.251ǁ	0.477ǁ	-0.356ǁ	0.041	0.235ǁ	-0.149	0.039	-0.032	-0.080	0.180	0.051	-0.149	0.244	0.300ǁ	0.369ǁ
Pupillomotor	-0.204	0.321ǁ	0.348ǁ	-0.141	0.241ǁ	0.377ǁ	-0.145	0.066	0.226	-0.091	0.047	0.113	0.087	0.350ǁ	0.323ǁ	0.344ǁ

Table 3. Correlation among K-COMPASS-31 scores, clinical features and the results of autonomic function tests

K-COMPASS-31 - Korean version of composite autonomic symptom score-31;
PRT - pressure recovery time; UPDRS - Unified Parkinson's disease rating scale;
H&Y - Modified Hoehn and Yahr; SCOPA-AUT - Scale for outcomes in Parkinson's disease-autonomic;
MMSE - mini-mental state examination; LEDD - levodopa equivalent daily dose;
NMSS - non-motor symptoms scale for Parkinson's disease;
PDQ-39 SI - Parkinson's disease questionnaire-39 summary index

*Spearman's rank correlation test.
‡Age-adjusted Spearman's partial rank correlation test
†Age and education years - adjusted Spearman's partial rank correlation test
§Age and UPDRS-III-adjusted Spearman's partial rank correlation test
ǁp value < 0.05

P41
Prevalence of apathy and its correlation with nigrosomal imaging in patients with Parkinson's disease

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Background: Apathy is a common yet neglected non motor symptom, which can be found at any stage of Parkinson's disease (PD). Apathy is associated with poor quality of life and increased care giver burden. Hence, recognition of apathy is important for treatment and care.
Methods: This was a single center prospective observational study, done in between October 2018 to October 2019. Parkinson's disease patients baseline data, UPDRS scores were recorded and assessed for presence of apathy using Lille apathy rating scale (LARS). Nigrosomal imaging, an imaging biomarker for PD was performed in few patients.
Results: 100 patients were included in this study. Twenty eight percent (28%) had apathy [14% each had moderate (grade 2) and severe grade(grade3)]. 13% had only mild signs of apathy (grade 1). Intellectual curiosity was the most affected subscore in our study (Mean= -1.99, SD=1.33).
No statistically difference was found between PD-Apathy and PD-Non Apathy groups in regards to age (p=0.32), age of onset (p=0.51), duration of symptoms (p=0.91), UPDRS scores and core clinical features. On comparison of normal PD patients and those with any grades of apathy, higher age (p=0.045), reduced alertness 30 min after awakening (p=0.014), longer time to get up in the morning (p=0.041) was seen in apathy group. Nigrosomal imaging was abnormal in 90% of patients. 40% patients had bilateral symmetrical nigrosome abnormality and 50% had abnormality on opposite side of onset of Parkinson disease symptoms. No correlation was noted with apathy
Conclusions: Apathy was prevalent in 28% of patients with Parkinson's disease. Intellectual curiosity subscore was the most effected one. No statistical difference was found between abnormality on Nigrosomal imaging with side of onset of disease and presence or absence of apathy.

P42
Short-latency afferent inhibition and the cholinergic system in Parkinson's disease

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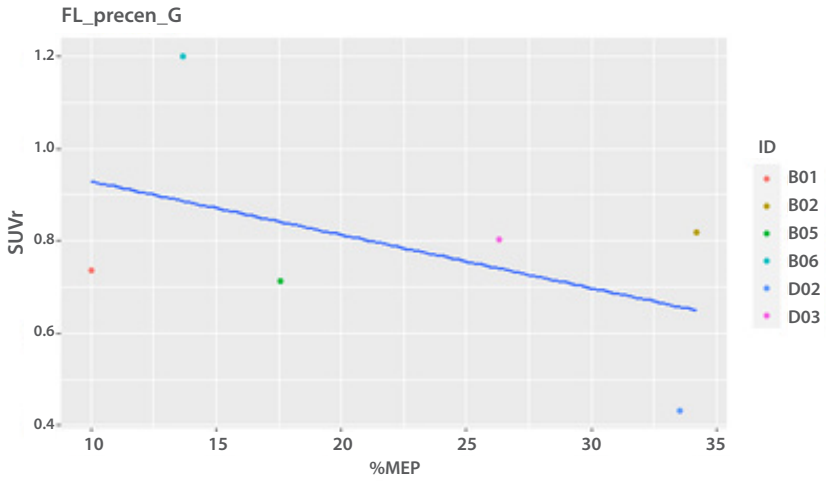
Background: Short-latency afferent inhibition (SAI) is often viewed as a cholinergic marker in Parkinson's disease (PD). Our objective is to assess the relationship between SAI and the cholinergic system integrity in patients with PD, using cholinergic PET imaging. Based on the working model of Turco et al. (2018), we expect the strongest relation in the primary motor cortex.
Methods: We performed both SAI and [18F]FEOBV PET imaging in PD patients. SAI was performed on the most affected side, using 5 different interstimulus intervals. A mean %MEP was calculated from the interval that showed the largest inhibition. Patients with clear tremor during the measurement were excluded from the analysis. SAI was correlated with [18F]FEOBV PET imaging in different brain areas, including the primary motor cortex (M1), primary somatosensory cortex (S1) and thalamus. The standardized uptake value ratio (SUVr) was calculated for each brain area, with cerebellar gray matter as a reference.
Results: Results from the first 6 subjects, all male, are presented (M1 shown in figure). Age of the individual subjects was 53, 61, 55, 76, 71 and 74. MoCA scores were 26, 27, 30, 26, 22 and 24, respectively. The data was fitted with a linear model. No statistical analysis was performed at this point due to the current lack of power.



Conclusions: We expect a negative relation between SUVr and %MEP. Linear regression shows a negative slope. However, no conclusions can be drawn at this point. Inclusion is ongoing and a healthy control group will be added for comparison.

P43
Personalised models to improve short-term detection of naturalistic motor fluctuations based on wrist-accelerometer data in Parkinson's disease

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Background: Adequate monitoring of motor fluctuations is essential for therapy evaluation in Parkinson's disease (PD). Traditional Parkinson evaluation tools are not applicable for real-life monitoring, and motion sensing is introduced to solve this. Several devices report promising augmentation of neurological decision making based on multiple day monitoring. The minimal period of time over which naturalistic motor fluctuations can be detected remains unanswered. Valid monitoring over shorter time windows is important for real-time monitoring applications. We hypothesise that personalised model training improves short-term validity of naturalistic motor fluctuation monitoring.
Methods: 20 PD patients were included, of which the side with the largest difference in unilateral upper extremity bradykinesia UPDRS III items between pre- and post-medication was analysed. 103 accelerometer features were extracted over 60 seconds windows. A support vector classifier was trained to differentiate between medication-states. Individual models were trained with 80% of a patient's data, and tested on the remaining 20%. Group models were trained on the other 19 patients' data, and tested on all data of one patient.
Results: Significant short-term classification of motor fluctuations was achieved in 75% of the patients. Individual and group models did not differ regarding mean AUC (both 0.70) and mean accuracy (respectively 65% and 64%). Significant individual model outcomes were slightly higher than significant group model outcomes. In the group model analyses, more included training patients and wider short-term windows led to better classification results.

Conclusions: Differentiation between naturalistic, short-term, motor fluctuations was possible in the majority of this PD population. Individual models did not show significant better results than group models. Short-term motor fluctuation detection with individual models should be further investigated with larger individual data sizes, and wider short-term feature windows, to determine the value of individual model training for PD motor monitoring. The wider windows have to serve the desired clinical real-time monitoring utilization.

P44
Effects of once-daily Opicapone 50 mg on the pharmacokinetics of Levodopa administered as Carbidopa/Levodopa extended-release capsules: An open-label phase 1 study

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Background: Opicapone (ONGENTYS®), a long-acting catechol-O-methyltransferase inhibitor, is approved as a once-daily adjunctive treatment to carbidopa/levodopa (CD/LD) in patients with Parkinson's disease (PD) experiencing OFF-episodes. It has been previously demonstrated that the addition of opicapone to immediate-release CD/LD decreases peak-to-trough fluctuation index, thus providing more consistent exposure to LD in patients with PD. Since there has been no prior evaluation of opicapone with the CD/LD extended-release (ER) formulation, a commonly used US clinical treatment, this study was conducted to assess the effects of opicapone 50 mg on the pharmacokinetics (PK) of LD and its metabolite, 3-*O*-methyldopa, when administered with oral CD/LD-ER capsules (RYTARY®; formerly IPX-066) in healthy individuals.
Methods: 18 healthy volunteers, (9 male, 9 female) ages 18-55 years, were included in this Phase 1 open-label study. CD/LD-ER 23.75/95 mg was administered as follows: 1 capsule three times a day (TID) on Days 1 and 16; 2 capsules TID on Days 2-3 and Days 17-18 every 7 hours at 07:00, 14:00, and 21:00. Opicapone 50 mg once daily was administered at 22:00 on Days 4-18. Blood samples for the assessment of PK parameters were collected on Days 3-4 (CD/LD-ER without opicapone) and Days 18-19 (CD/LD-ER with opicapone) every 30 minutes from 07:00 to 21:00 and every 2 hours from 23:00 until 09:00 the next morning.
Results: Findings will be presented at the meeting.
Conclusions: It is expected that adding once-daily opicapone to CD/LD-ER will result in increased LD concentration at every time point, with higher trough concentrations and further decreases in peak-to-trough fluctuations. This approach may provide more consistent exposure to LD, which continues to be an essential treatment strategy for PD patients with motor fluctuations.

Parkinson Disease: Therapy (excluding surgical, physical)

P45
Gene expression in the frontal cortex is bilaterally affected by L-DOPA in rats with unilateral 6-hydroxydopamine lesions

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Background: The primary goal of L-DOPA treatment in patients with Parkinson's disease is to restore dopamine signaling in the basal ganglia and alleviate the motor symptoms of the disease. However, the effects of L-DOPA extend beyond the basal ganglia, which has major impact on the treatment of the non-motor symptoms of the disease. Here we investigated how L-DOPA alters gene expression within the frontal cortex of rats with unilateral lesions of the ascending dopaminergic transmission.

Methods: Lesion of dopaminergic nigrostriatal pathway was induced in male rats with 6-hydroxydopamine (8 ug/4 ul) infused into the left medial forebrain bundle. Animals were then treated with L-DOPA (12.5 mg/kg) and benserazide hydrochloride (6.25 mg/kg) or saline for 14 days. The rats were killed and their frontal cortex tissue from both hemispheres was dissected separately and used for RNA extraction. Next, we performed RNA-seq and analyzed the results for differentially expressed genes, gene coexpression and functional annotation of the implicated genes.

Results: We identified 48 genes with L-DOPA-induced transcript abundance changes. These were functionally diverse and expressed in multiple cell types. There were no gene-level expression changes between the hemispheres, however, one of the *Mmp9* mRNA isoforms was upregulated on the contralateral side. Gene coexpression analysis lead to identification of 5 gene clusters. One of them contained immediate-early genes and was highly overlapping with the differentially expressed genes. Both differentially expressed genes and the genes within the immediate-early gene cluster had similar transcription profiles to those induced by other types of drugs.

Conclusions: Chronic L-DOPA treatment has a robust and predominantly bilateral effect on gene expression within the frontal cortex in the unilaterally 6-hydroxydopamine-lesioned rats. Notably, the changes in expression likely also affect several types of non-neuronal cells in the cortex and with only a few exceptions are not specific to L-DOPA.

P46
Non-Motor Symptoms Burden Groups in Parkinson's Disease. Change after treatment with safinamide

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Background: In Parkinson´s disease (PD) patients, non-motor symptoms burden (NMSB) can be classified as mild (Non-Motor Symptoms Scale [NMSS] 1-20), moderate (NMSS 21-40), severe (NMSS 41-70), and very severe (NMSS > 70).
The aim of this study was to analyze the change in NMSB of PD patients from the SAFINON-MOTOR study, a Spanish multicenter open-label study for assessing the effectiveness of safinamide on NMS at 6 months.
Methods: PD patients with a severe or very severe NMSB burden at baseline (NMSS > 40) were included. NMSB was assessed at V1 (baseline), V2 (1 months ± 7 days), V3 (3 months ± 15 days) and V4 (6 months ± 15 days, end of the Observational Period).
Results: 50 patients were included between May/2019 and February/2020 (age 68.5 ± 9.12 years; 58% women; 6.4 ± 5.1 years from diagnosis). At 6 months, 44 patients completed the follow-up (88%). The NMSS total score was reduced by 38.5% (from 97.5 ± 43.7 in V1 to 59.9 ± 35.5 in V4; p <0.0001). NMSB was: at V1, 32% severe and 68% very severe (N=50); at V2, 8.7% mild, 23.4% moderate, 23.4% severe, and 44.7% very severe (N=47); at V3, 8.9% mild, 22.3% moderate, 33.3% severe, and 45.5% very severe (N=45); at V4, 6.8% mild, 25% moderate, 34.1% severe, and 34.1% very severe (N=44). From V1 to V4, 54.5% (24/44) of the patients changed to an inferior NMBS group whereas only 1 patient changed to a superior NMSB group.
Conclusions: Safinamide improves NMSB in PD patients.

P47
Natural levodopa consumption and improved balance score in a patient with Parkinson's disease: A case study

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Background: *Mucuna pruriens* is rich in natural levodopa, reported to be tolerated and has been an effective treatment for Parkinson's disease. We report the case of a 66 year old elderly male diagnosed with PD for 8 years, residing in Ernakulam district of Kerala, India. This is the first reported case of a PD patient with a Berg Balance score of 56 despite an eight year diagnosis.
Methods: The case was interviewed using a semi-structured questionnaire to understand the demographic data, risk factors, history of falls, medication, balance, and level of functioning.
Results: The patient was assessed as Stage 2.0 (bilateral involvement without impairment of balance) by Hoehn and Yahr staging scale. A higher ABC score of 85.62% further classified him to have a high level functioning and higher confidence. An interesting finding from the study was a reduced intake of Syndopa plus to half a tablet per day and incorporation of *Mucuna pruriens* seed in powdered 4g twice to the daily medication schedule. He self-reported to have better balance throughout the day and felt that consumption of natural levodopa to be the reason for his better gait and postural instability.
Conclusions: The case highlighted better balance scores and level of functioning with regard to lesser synthetic drug consumption and more Mucuna pruriens consumption. This unique case study is being reported for further studies to be taken up by researchers to understand symptom alleviation and its association with the natural levodopa in powdered form, *Mucuna pruriens*. This can be of paramount importance as many synthetic drugs have reported to cause various side effects which further deteriorate their quality of life.
The report on this intrinsic case study focusing on balance, Mucuna pruriens and severity is unique and would definitely help in further research expansion thereby improving overall disease management strategies among PD patients.

P48
BouNDless: An active-controlled randomized, double-blind double-dummy study of continuous ND0612 infusion in patients with fluctuating Parkinson's disease

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Background: ND0612 is an investigational subcutaneous (SC) delivery system providing minimally invasive, continuous infusion of liquid levodopa/carbidopa for patients with PD experiencing motor fluctuations. The aim of this study is to establish the efficacy, safety, and tolerability of ND0612 in comparison to oral levodopa/carbidopa (IR LD/CD) in patients with PD experiencing motor fluctuations.
Methods: BouNDless is a multicenter, randomized, active-controlled, double-blind, double-dummy, parallel group clinical trial. Key eligibility criteria: PD patients (Hoehn and Yahr ≤ 3) on ≥ 4 doses/day of CD/LD oral therapy (≥ 400 mg of LD), experiencing motor fluctuations (average of ≥ 2.5 hours of OFF time during waking hours). The ongoing study comprises 6 periods:
Period 1: Screening (1-4 weeks);
Period 2: Open-label oral CD/LD adjustment period (4-6 weeks);
Period 3: Open-label ND0612 conversion period (4-6 weeks);
Period 4: Double-blind, double-dummy, active-controlled, maintenance period where patients are randomized to either ND0612 infusion + Dummy IR CD/LD, OR to Dummy infusion + IR CD/LD (12 weeks);
Period 5: Optional open-label extension period (1-year);
Period 6: Safety follow-up (12 weeks).
Results: The primary endpoint is the change from Baseline (randomization) to end of the maintenance period (Week 12) in mean ON time without troublesome dyskinesia, normalized to 16 waking hours, using patient-rated ON/OFF diary assessments. Secondary outcome measures include changes in: OFF time (key secondary), UPDRS (Parts II and III), Patient's and Clinician's Global Impressions of Change, ON time without dyskinesia, PDQ-39 and Parkinson's Disease Sleep Scale (PDSS) scores. Safety and tolerability are assessed via adverse event reporting, including local skin safety assessments, rates of premature discontinuation, and study treatment compliance.
Conclusions: BouNDless is the first Phase III study designed to assess the efficacy and safety of treatment with ND0612 in comparison to oral immediate-release LD/CD in patients with PD experiencing motor fluctuations.

P49
Frequency of respiratory comorbidities in patients with Parkinson's disease

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Background: Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease with widespread effects. Some respiratory disorders may occur in individuals with PD and may contribute to morbidity and mortality and affect PD treatment choices. We evaluated the frequency of respiratory comorbidities in a cohort of patients with PD.
Methods: This was a longitudinal claims data analysis of the IQVIA PharMetrics® Plus database, a closed database of adjudicated medical and pharmacy claims in the United States. The analysis cohort included patients who had continuous medical and pharmacy benefits from 2016–2018 with ≥1 diagnosis of PD (International Classification of Diseases, 10th Revision [ICD-10], Clinical Modification code G20) with record types of management, surgery, facility, or pharmacy, and ≥1 pharmacy claim for carbidopa/levodopa in the study period. After cohort identification, the frequencies of mild and severe respiratory comorbidities were evaluated based on ICD-10 and clinical expert categorizations. The respiratory comorbidities were further categorized as acute or chronic.
Results: Of 8192 patients, 64% were men and median age was 65 years. The frequency of any respiratory comorbidity was 49%. Any chronic respiratory comorbidity occurred in 19% of patients and included asthma, chronic obstructive pulmonary disease, snoring, chronic emphysema, chronic bronchitis, chronic respiratory failure, pulmonary fibrosis, cystic fibrosis, and other breathing abnormalities. The frequency of any acute respiratory comorbidity was 43% and included cough, acute bronchitis, shortness of breath, pneumonia, dyspnea, acute respiratory failure, hypoxemia, and wheezing. Of the 8192 patients, 15% had chronic, severe respiratory comorbidities and 5% had chronic, mild respiratory comorbidities. Acute, severe respiratory comorbidities and acute, mild respiratory comorbidities occurred in 23% and 35%, respectively.
Conclusions: In this cohort of patients with PD, both chronic and acute respiratory comorbidities were common, included a broad spectrum of conditions, and were severe in over 30% of patients when combined.

P50
Safety and tolerability of ND0612 in patients with Parkinson's disease experiencing motor complications: One year results from the BeyoND study

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Background: ND0612 is an investigational subcutaneous (SC) delivery system providing minimally invasive, continuous infusion of liquid levodopa/carbidopa for patients with Parkinson's disease (PD) experiencing motor fluctuations.
The primary objective of this phase 2b study was to evaluate the long-term safety and tolerability of a 24-hour dosing regimen and a 16-hour 'waking day' regimen of ND0612.
Methods: The BeyoND study (NCT02726386) is an ongoing international, open-label Phase 2b study evaluating the long-term safety of two ND0612 dosing regimens in patients with PD (H&Y ≤3 during ON) taking ≥4 levodopa doses/day and ≥1 other PD medications, and experiencing ≥2 hours of OFF time/day with predictable early-morning OFF periods.
Results: Of the 276 patients screened, 214 were enrolled (24-hour dosing regimen: n=90; 16-hour regimen: n=124) and 120 (56%) completed 12 months treatment. Leading causes for discontinuation were consent withdrawal (n=42, 19.6%) and AEs (n=38 [17.8%] including infusion site reactions n=22 [10.3%]). Discontinuation rates decreased after a protocol amendment and extensive training on appropriate patient selection and expected infusion site reactions (49% early terminations prior to the amendment vs 29% following the amendment).
Most patients had an infusion site reaction; the most common reactions considered as adverse events were nodules (n=66, 30.8%), hematoma (n=54, 25.2%) and infusion site pain (n=28, 13.1%). Other common adverse events were falls and urinary tract infection (each n=20, 9.3%) and dyskinesia (n=16, 7.5%).
Conclusions: ND0612 infusion was found to be safe with generally mild to moderate infusion site reactions typical for a subcutaneous mode of continuous drug delivery and no unexpected TEAEs for systemic levodopa treatment. Long-term data will continue to be collected in patients enrolled in the study extension, some of whom are now in their fifth year of ND0612 treatment.

P51
Moderate aerobic exercise improve motor symptoms in Parkinson's disease by Microbiota - Gut-Brain axis

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Background: Recently, increasing evidence has suggested the association between physical exercise and Parkinson's disease (PD) rehabilitation, previous studies provided a potential mechanistic link between gut microbiota dysbiosis and neuroinflammation in PD progression. However, whether exercise improvement the disorder of PD through the gut microbiota- peripheral inflammatory- neuroinflammation to be explored.
Methods: 30 animals were divided into thress groups: control group, MPTP group and exercised MPTP group (PD+EX). After 10 times MPTP injections , PD+ EX gorop was forced to run on a motorized treadmill for 12 consecutive weeks. Fecal samples were collected to was Sequenced by 16S rDNA. and the exercised PD patients and exercised PD mouse peripheral blood RNA sequence were uesd to analyzed.
Results:

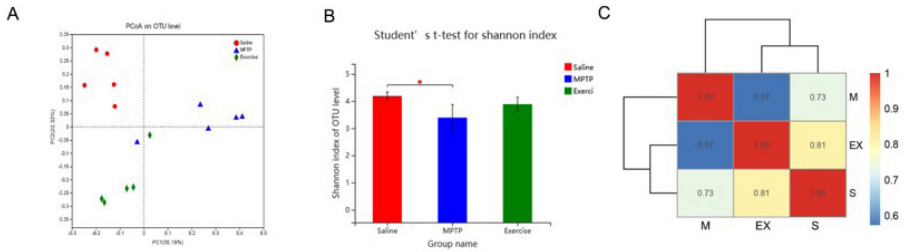

Figure. Analysis of bacterial 16S rDNA from gut microbiota of PD mice shows exercise reduces PD microbial dysbiosis. (A) PCoA plots based on weighted UniFrac metrics of gut microbiota. (B) Analysis of alpha diversity-predicted diversity of gut microbiota by shannon estimator analysis. (C) Heatmap based on the Bray-Curtis distance analysis about relative abundance of gut microbiota at the OTU level in three groups. n = 5 mice per group.

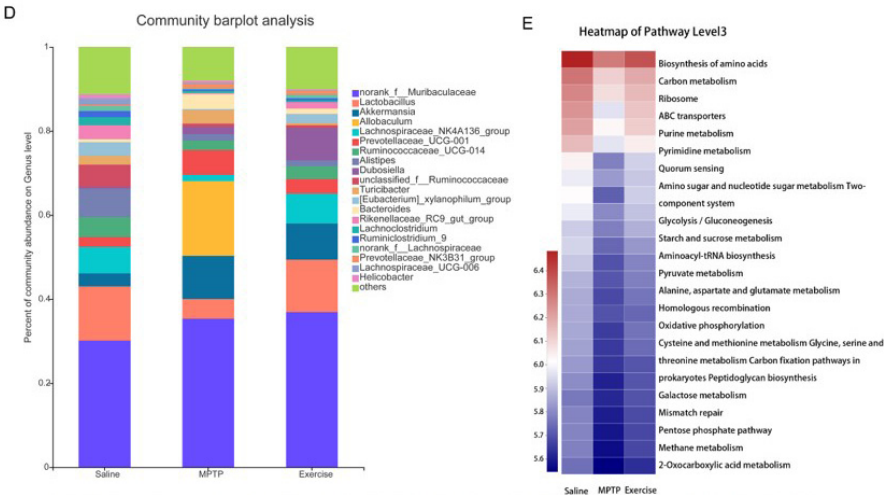

Figure. Analysis of bacterial 16S rDNA from gut microbiota of PD mice shows exercise reduces PD microbial dysbiosis. (D) Distribution of relative abundance of gut microbiota at the genus level observed in the three groups. n = 5 mice per group.

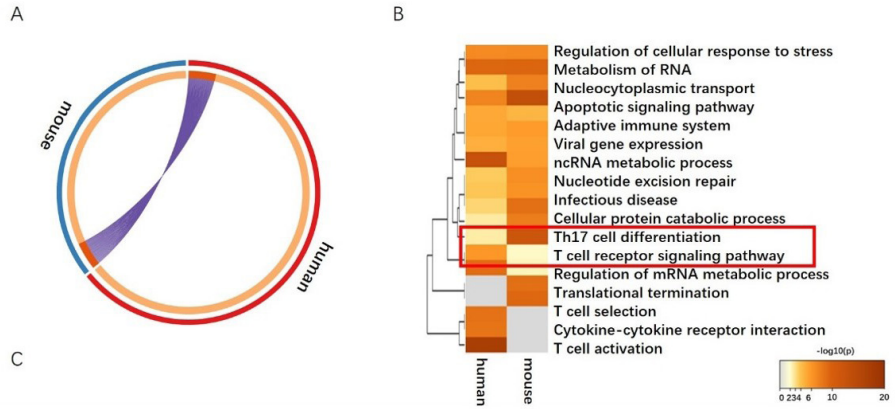

Figure. Peripheral blood RNA profile between human and mouse. (A) The circos plot shows how genes from the input gene lists overlap between human and mouse peripheral blood. (B) Enrichment_heatmap_HeatmapSelectedGOTop20 between human and mouse peripheral blood.

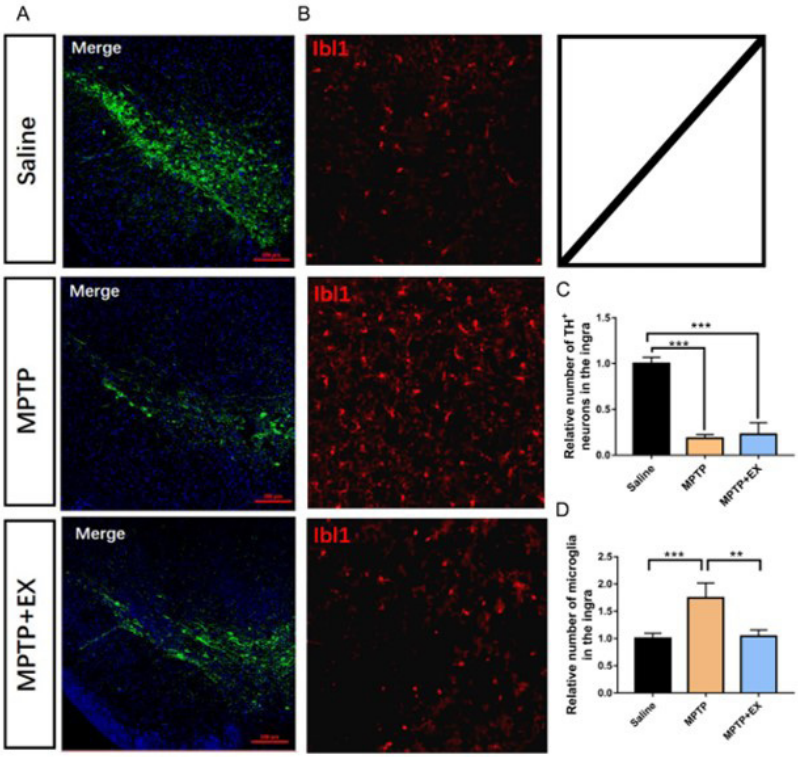

Figure. Exercise treatment of mice reduced the glial-mediated neuroinflammation in brain. (A) Representative IF staining for TH (dopaminergic neuron marker) in the SN. Scale bar is 200μm. (C) Quantitative analysis of the number of TH-positive cells in the SN. (B) Representative IF staining for Ibal-1 (microglia marker) in the SN. Scale bar is 100μm. (D) Quantitative analysis of the number of Ibal-1-positive cells in the SN.

Conclusions: Moderate Aerobic Exercise improve motor symptoms in Parkinson's disease by Microbiota- Gut-Brain axis.

P52
Safety and efficacy of istradefylline, an A_{2A} receptor antagonist, in Parkinson's disease: Results from pooled analyses

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Background: Istradefylline, a selective adenosine A_{2A} receptor antagonist, is indicated in the USA and Japan as adjunctive treatment to levodopa/decarboxylase inhibitors in adults with Parkinson's disease (PD) experiencing OFF-time.

This pooled analysis from multiple trials further characterized the occurrence and impact of dyskinesia.

Methods: In 8 randomized, placebo-controlled, double-blind, phase 2b/3 trials, patients received istradefylline (this analysis included only 20 or 40mg/day treatment arms) or placebo for 12 or 16 weeks. Three studies did not assess the UPDRS-IV query for painful dyskinesia (painful-dysk, item 34); painful-dysk was therefore evaluated in only the five studies reporting this endpoint.

Primary endpoints were change from baseline in OFF-time (istradefylline vs placebo) based on patient-completed 24-hour ON/OFF diaries; subgroups with (+BL-dyskinesia) and without (–BL-dyskinesia) BL-dyskinesia were defined using these diaries. Adverse events (AEs) were recorded as spontaneous reports.

Results: Dyskinesia AEs were more frequent with istradefylline than placebo in +BL-dyskinesia (20mg/day, 120/486 [24.7%]; 40mg/day, 119/460 [25.9%]; placebo, 80/569 [14.1%]) and –BL-dyskinesia (16/362 [4.4%]; 35/419 [8.4%]; 15/423 [3.5%]) subgroups. Reduction in OFF-time and increase in ON-time without troublesome dyskinesia (ON-WOTD) were greater with istradefylline than placebo and unaffected by BL-dyskinesia. At baseline, 89.3% (1307/1464) of patients reported no painful-dysk.

Among patients with painful-dysk and data available at endpoint, absence of painful-dysk at endpoint occurred in 95.6% (348/364), 95.8% (452/472), and 95.9% (450/469) of those treated with 20mg/day istradefylline, 40mg/day istradefylline, and placebo, respectively.

Conclusions: Dyskinesia was more frequent during istradefylline treatment but relatively infrequently reported in the –BL-dyskinesia subgroup. Istradefylline-induced improvements in OFF- and ON-WOTD-time were not affected by BL-dyskinesia. Patients with no painful-dysk at

baseline remained free of painful-dysk at the study endpoint. While interpretation is limited by the relatively small number of patients reporting painful-dysk before and/or during istradefylline treatment, results suggest further research is warranted.
Supported by Kyowa Kirin Co., Ltd.

P53
Butylphthalide suppresses erastin-induced ferroptotic cell death of dopaminergic neurons

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Background: Ferroptosis is a novel regulated iron dependent cell death pathway, which is characterized by lethal accumulation of lipid peroxides in cells. Recent studies have shown that the signal pathway of ferroptosis is consistent with several pathophysiological characteristics of Parkinson's disease (PD). Thus, the application of safe and effective drugs to modulate ferropotosis may be a promising strategy for the treatment of PD. DL-3-n-butylphthalide (NBP), an extract of celery, is commonly used for cerebral ischemia treatment. Based on its broad pharmacologic effects, more and more clinical researches about neurodegenerative diseases are also focused on NBP.
The present study was to investigate whether NBP pretreatment suppressed erastin-induced ferroptosis in MES23.5 cells (rat dopaminergic neurons).
Methods: MES23.5 cells were pretreated with NBP (25 -100 μM) for 2 hours, followed by erastin (20μM) for another 24h. Then CCK-8 assay was used to assess the erastin-induced cytotoxity.
Results: Here, we demonstrated that the viability of MES23.5 cells decreased after treatment with erastin compared with the blank group, which could be reversed by the pretreatment of NBP. As it is indicated that lipid peroxidation is one of the indicators for ferroptosis, we further used 2′,7′-Dichlorodihydrofluorescein diacetate (DCFH-DA) staining and C11-BODIPY staining to detect intracellular ROS and membrane lipid peroxidation, respectively.
The results suggested that erastin treatment significantly increased intracellular ROS and lipid peroxidation in MES23.5 cells, while NBP obviously reduced intracellular ROS and lipid peroxidation in MES23.5 cells treated by erastin.
Conclusions: Collectively, these findings indicate that NBP confers protection on erastin-induced MES23.5 cells partially via reducing iron-mediated production of lipid reactive oxygen species.

P54
LRRK2 inhibition by BIIB122 / DNL151 in double-blind, placebo-controlled Phase 1 healthy volunteer and Phase 1B Parkinson's disease trials

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Background: Objective: To evaluate safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of the LRRK2 inhibitor, DNL151 (BIIB122), in healthy volunteers (HVs) and Parkinson's disease (PD) patients.

Background: Improving lysosomal function through inhibition of LRRK2 kinase is a promising therapeutic approach for PD. DNL151 is a potent, selective, CNS-penetrant LRRK2 kinase inhibitor under

investigation for the treatment of PD.

Methods: Safety, tolerability, PK and pharmacodynamics of DNL151 are being evaluated in two studies. DNLI-C-0001 is an ongoing double-blind, placebo-controlled Phase 1 single- and multipleascending dose HV trial evaluating a broad dosing range up to 28 days. DNLI-C-0003 is a multicenter, double-blind, placebo-controlled, Phase 1b PD patient trial evaluating 3 dose levels over 28 days. Safety assessments in both studies include vital signs, ECGs, laboratory tests, pulmonary function testing, and adverse events (AEs).

Biomarker outcomes include serine 935 phosphorylation of LRRK2 in whole-blood (pS935-LRRK2) for target engagement; threonine 73 phosphorylation of Rab10 in PBMCs (pT73-pRab10) for pathway engagement; and urine bis(monoacylglycerol)phosphate (BMP), a measure of lysosomal function downstream of LRRK2.

Results: DNLI-C-0001 randomized 186 HVs and DNLI-C-0003 randomized 36 PD patients. DNL151 has been generally well tolerated in both studies. No serious adverse events reported; 85% of HVs to date and 73% of PD on active treatment experienced AE's, the majority of which were mild in severity. One HV subject discontinued early in DNLI-C-0001 due to moderate nausea, headache, impaired concentration and diarrhea. Two PD patients discontinued early in DNLI-C-0003 due to hypotension or orthostatic hypotension; both resolved without intervention. At well tolerated doses in HVs and PD patients, a median, time-averaged reduction up to ~85% in pS935-LRRK2 and pT73-Rab10 as well as a reduction in urine BMP were observed.

Conclusions: LRRK2 inhibition with DNL151 demonstrated dose-dependent target and lysosomal pathway engagement at doses generally well-tolerated in HVs and PD patients. These results support continued investigation of LRRK2 inhibition with DNL151 for the treatment of PD.

Parkinson Disease: Other topics

P55
Falls predict acute hospitalization in Parkinson's Disease

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Background: The aim of the present study was to identify predictors of acute unplanned hospitalization in Parkinson´s disease (PD).
Methods: PD patients recruited from 35 centers of Spain from the COPPADIS cohort from January 2016, to November 2017, were included in the study. Patient baseline evaluation included motor assessment, non-motor symptoms (NMS), cognition, mood and neuropsychiatric symptoms, disability, and quality of life. Kaplan-Meier estimates were obtained and Cox regression performed on time to hospital encounter 1-year after the baseline visit.
Results: Thirty-five out of 605 (5.8%) PD patients (62.5 ± 8.9 years old; 59.8% males) presented an acute unplanned hospitalization during the 1-year follow-up after the baseline visit. Traumatic falls (9 events) represented the most frequent cause of admission, being 56.3% of

all indirect disease related PD morbidity causes and 23.7% and 18.4% of all acute unplanned (38 events) and all hospitalizations (49 events), respectively. To suffer from motor fluctuations (HR [hazard ratio] 2.461; 95% CI, 1.065-5.678; p=0.035), a very severe NMS burden (HR [hazard ratio] 2.828; 95% CI, 1.319-6.063; p=0.008), falls (HR 3.966; 95% CI 1.757-8.470; p=0.001), and dysphagia (HR 2.356; 95% CI 1.124-4.941; p=0.023) was associated with acute hospitalization after adjustment to age, gender, disease duration, levodopa equivalent daily dose, total number of non-antiparkinsonian drugs, and UPDRS-III-OFF.
Of the previous variables, only falls (HR 2.998; 95% CI 1.080-8.322; p=0.035) was an independent predictor of acute hospitalization.
Conclusions: Falls is an independent predictor of acute unplanned hospitalization in PD patients.

P56
Apomorphine sublingual film for the treatment of "OFF" episodes in patients with Parkinson's disease: Impact on impulse control disorders

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Background: In a 12-week pivotal controlled (PC) study, apomorphine sublingual film (APL) was efficacious and generally well-tolerated for on-demand treatment of "OFF" episodes in patients with Parkinson's disease (PD). Herein, we evaluated effects of APL on impulse control disorders (ICDs).
Methods: Patients with PD and "OFF" episodes on stable PD medications (eg, oral/transdermal dopamine agonists) participated in the PC (NCT02469090) and/or ongoing long-term safety (LTS; NCT02542696) studies. Patients in practically defined "OFF" received APL (optimized dose [10–35 mg] that resulted in a FULL "ON" within 45 minutes during open-label titration) or matching placebo for ≤5 "OFF" episodes/day over 12 weeks (PC study) or open-label APL for 48 weeks (LTS study). ICDs were assessed using the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS) and summarized descriptively.
Results: Analysis included 109 patients in the PC study (APL, n=54 [2.2 mean doses/day]; placebo, n=55 [2.5 doses/day]) and 345 in the LTS study (data cut May 2019: 1.8 doses/day). In the PC study, mean baseline total ICD scores were 5.4 for APL and 6.3 for placebo; week 12 changes from baseline were –1.3 and –1.5. Baseline total QUIP-RS scores were 9.2 and 11.8; week 12 changes from baseline were –0.8 and –2.8. For APL, individual ICDs decreased or remained

similar from screening to week 12, except for gambling. In the LTS study, mean baseline total ICD score was 5.7; changes from baseline were –0.3, –1.6, and 0.6 at weeks 24, 36, and 48. Baseline total QUIP-RS score was 10.6; changes from baseline were –1.7, –4.8, and 0.3 at weeks 24, 36, and 48.
All individual ICDs either decreased or remained similar from screening to week 48.
Conclusions: On-demand treatment with apomorphine sublingual film for "OFF" episodes in patients with PD had minimal impact on ICDs for up to 48 weeks.

P57
Apomorphine sublingual film for the treatment of "OFF" episodes in patients with Parkinson's disease: Impact on dyskinesia

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Background: In a 12-week pivotal controlled (PC) study, apomorphine sublingual film (APL) was efficacious and generally well-tolerated for on-demand treatment of "OFF" episodes in patients with Parkinson's disease (PD). Herein, we assessed impact of APL on time spent with/functional impact of dyskinesia.
Methods: Patients with PD and "OFF" episodes on stable PD medications (eg, oral/transdermal dopamine agonists) participated in the PC (NCT02469090) and/or ongoing long-term safety (LTS; NCT02542696) studies. Patients in practically defined "OFF" received APL (optimized dose [10–35 mg] that resulted in FULL "ON" within 45 minutes during open-label titration) or matching placebo for ≤5 "OFF" episodes/day over 12 weeks (PC study) or open-label APL for 48 weeks (LTS study). Dyskinesia was assessed using MDS-UPDRS Part IV and summarized descriptively.
Results: Analysis included 109 patients in the PC study (APL, n=54 [2.2 mean doses/day]; placebo, n=55 [2.5 doses/day]) and 345 in the LTS study (data cut May 2019: 1.8 doses/day). In the PC study, mean percent time with dyskinesia at week 12 decreased with APL and increased with placebo (-2.82% vs +5.95%). APL resulted in less worsening of dyskinesia (12% vs 25%). More APL-treated patients reported "Improved" vs "Worsened" for time spent with dyskinesia (15% vs 12%). In the LTS study, more patients at week 24 reported "Improved"/"No change" vs "Worsening" from baseline in time spent with dyskinesia (19%/65% vs 16%) and functional impact of dyskinesia (18%/65% vs 17%); results were similar at weeks 36 and 48. TEAEs of dyskinesia were not reported in the PC study and occurred in 7% (28/425) in the LTS study, with no apparent dose relationship.

Conclusions: On-demand treatment with apomorphine sublingual film for "OFF" episodes resulted in reduced time spent with dyskinesia at 12 weeks vs placebo and higher rates of "Improved"/"No change" vs "Worsening" dyskinesia for up to 48 weeks.

P58
Detecting bradykinesia in morning "OFF": A database study using the Personal KinetiGraph®

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Background: Patients with Parkinson's disease (PD) often experience "OFF" episodes including morning "OFF" (akinesia or bradykinesia before the first daily dose of carbidopa/levodopa [CD/LD]). We used the Personal KinetiGraph® (PKG) system to examine bradykinesia and morning "OFF."
Methods: De-identified data from PKGs performed in routine clinical care (clinics with >45 individuals with PD) were obtained and analyzed. A computational model used PKG data from the first morning dose to predict the absolute change in Unified Parkinson's Disease Rating Scale (UPDRS) Part III scores from a CD/LD challenge test. The UPDRS Part III scale was divided into 6 severity levels (0–5; 5 = highest severity) to categorically classify motor function. An algorithm based on a logistic regression model of UPDRS Part III scores, measured before and after a CD/LD dose, was developed that categorized each 2-minute PKG recording (epoch) between 09:00–18:00 into 1 of the 6 severity levels to measure the proportion of time an individual spent in bradykinesia and his/her response to CD/LD. The proportion with median bradykinesia scores above target (severity ≥2.5, equivalent to UPDRS Part III score ≥35), CD/LD responsiveness (≥1.15 decrease in severity level postdose, corresponding to ~14-point reduction in UPDRS Part III score), and the prevalence of morning "OFF" were determined from available epochs.
Results: Of 12,840 individuals with PD (US: n=3288; EU: n=9552), median bradykinesia scores were above target in 55% and significantly higher in US vs EU individuals (65% vs 54%; $P<0.0001$). In US individuals, the prevalence of morning bradykinesia was 85%, and bradykinesia persisted in ~64% after the morning CD/LD dose.
Conclusions: Many patients in the US have morning "OFF," may be undertreated or experience limited beneficial response to their morning CD/LD dose, and may therefore benefit from optimization of their current treatment regimen or addition of adjunctive treatment options.

P59

Analysis of MRI results in Parkinson's disease, vascular Parkinsonism and chronic cerebral ischemia

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Objective: To identify differences in the results of brain tomography in Parkinson's disease (PD), Vascular Parkinsonism (VP) and Chronic cerebral ischemia (CCI).
Methods: The examination was conducted in the neurology department of TMA. All patients underwent a clinical neurological examination. MRI results of patients were analyzed. Patients were studied in 3 groups.
1. 68 with PD
2. 65 with VP
3. 65 patients with CCI participated in the study.
Results: According to the results of a comparative analysis of patients and control group of volunteers:
Mild cerebral atrophy was observed in 64.3 ± 3.3% of patients in the PD group, 100% in the VP group, in 37.3% of patients in the CCI group and flattening of the cerebral hemispheres in 16.2 ± 2.1% of patients with PD, 26.6 ± 1.1% of patients with VP, 9.3 ± 3.3% of patients with CCI were also noted.
Similar results were recorded mainly in the group of patients with PD and CCI, mild periventricular edema was reported in 49.7 ± 2.1% of patients in PD, 62.4 ± 1.3% in VP, and 55.7 ± 3.4% in patients with CCI. Also, subcortical leukoareosis was observed separately and in small localities at 79.4 ± 3.2 hyperintensity in different localizations in 51,4% in group 1, 74.8% in group 2, 49.3% in the third group, ischemic change of subcortical nuclei in the first group was 49.2 %, in the second group was 76.2%, in the third group was 38.9%.
Conclusions: The obtained results show that the role of brain tomography in the analysis of PD and VP transmission is high. Although the clinical symptoms of PD and VP were similar, the etiopathogenesis of the disease in these two pathological conditions was different, and MRI changes in CCI proved to be the same as in mild levels of VP.

P60
Efficacy of Opicapone in the reduction of ON-time with troublesome Dyskinesia in PD patients with motor fluctuations and troublesome dyskinesia

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Background: Opicapone is a once-daily catechol-O-methyltransferase inhibitor approved as adjunctive treatment to levodopa/carbidopa in Parkinson's disease (PD) patients experiencing OFF episodes. Analyses were conducted to evaluate ON-time with troublesome dyskinesia (frequently called ´Bad ON-time') and ON-time without or with non-troublesome dyskinesia ('Good ON-time') following long-term opicapone exposure in PD patients with motor fluctuations and troublesome dyskinesia at baseline.
Methods: Matching efficacy data from BIPARK-1 and -2 were combined for opicapone 50 mg. The studies had similar designs, eligibility criteria, and methodologies. Primary efficacy endpoint was change from baseline in OFF-time based on patient diaries. This *post-hoc* analysis evaluated the long-term effect of opicapone 50 mg on 'Bad ON-time' and 'Good ON-time' in patients with >2 hours of troublesome dyskinesia at baseline.
Results: Of 216 patients in the Full Analysis Set, 44 (20.4%) had >2 hours of troublesome dyskinesia at baseline. At end of the double-blind period (~3.5 months), 'Good ON-time' increased with opicapone 50 mg and 'Bad ON-time' decreased, with an overall mean levodopa reduction of ~40 mg/day (see figure next page).
At end of the 1-year open-label extension (OLE) period, mean daily 'Good ON-time' increased by ~2 hours, 'Bad ON-time' decreased by ~1 hour, and mean daily levodopa dose decreased by an additional 60 mg.
Conclusions: In PD patients with motor fluctuations and reporting troublesome dyskinesia, exposure to opicapone for almost 1 year was associated with reduced levodopa dose, reduced ON-time with troublesome dyskinesia, and increased ON-time with no/non-troublesome dyskinesia.

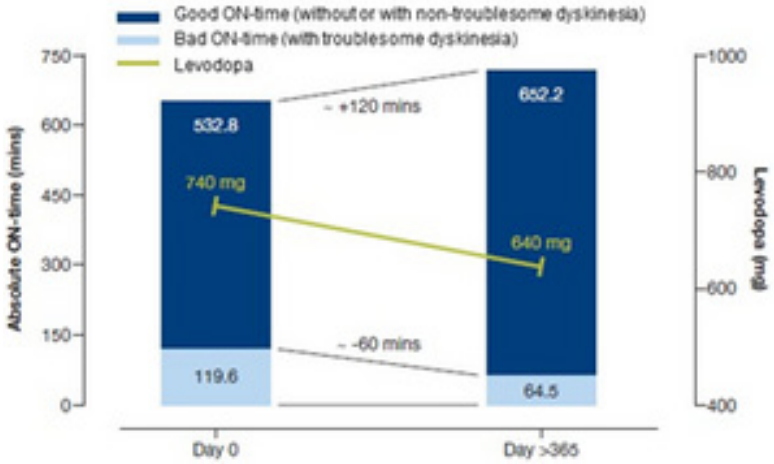

Figure. Evolution of Absolute ON-time following initiation with opicapone 50mg in patients with parkinson's disease with motor fluctuations and reporting troublesome dyskinesia

P61
Characterizing the role of genetic variants influencing α-synuclein seeding activity using neuropathologically characterized human brains

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Background: Parkinson's disease (PD), Dementia with Lewy bodies (DLB), and Multiple system atrophy (MSA) are all synucleinopathies, which are characterized by the accumulation of **p**athological **α-s**ynuclein (pα-syn) protein aggregates in the brain. Differing pathological presentations in PD, DLB, and MSA result in distinct clinical phenotypes between diseases. Neuropathologic examination of human brains reports compelling evidence on the existence of distinct pα-syn strains between disease types. These strains can be used as a molecular biomarker to distinguish between diseases; however, neither the role of genetic variants nor the distribution of pα-syn strains across susceptible brain regions in PD, DLB, and MSA have been defined

Methods: Real-time quaking-induced conversion (RT-QuIC) is an ultrasensitive detection technology for quantifying and characterizing misfolded proteins and has greater sensitivity and specificity compared to conventional approaches, such as immunohistochemistry. RT-QuIC has been used to detect paS in the brain and cerebrospinal fluid (CSF) from PD and MSA and has a sensitivity and specificity level ranging from 95-100%.
We have optimized the RT-QuIC assay to assess large cohorts of pathologically confirmed diseased brain tissues to explore pα-syn seeding activity in synucleinopathies, and whether pα-syn is a suitable biomarker of disease type and progression
Results: We have generated quantitative measures of α-synuclein seeding kinetics using RT-QuIC assays to characterize pα-syn strains in PD, DLB, and MSA brains. These measures have been overlayed with available genomic and clinical data to determine genetic markers influencing pa-syn levels and have explored how pa-syn measures influence clinical phenotypes.
We will identify if key genetic variation may influence the aggregation profiles of individual subjects
Conclusions: The data from this ongoing study demonstrates that paS is a suitable biomarker to examine in neuropathologically characterized human brains, using RT-QuIC technologies.

P62
Is directional stimulation more cost-effective than omnidirectional stimulation in Parkinson's disease?

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Background: The technique of deep brain stimulation (DBS) has recently undergone a remarkable improvement. The development of directional electrodes is one of the most important milestones in this technical evolution.
Although continuously evolving data supports the fact that directional subthalamic DBS has a wider therapeutic window, lower therapeutic current strength, and better normalized therapeutic window percentage, no comparative studies have been conducted on the level of postoperative reduction in the daily dose of oral antiparkinsonian medications after directional versus omnidirectional DBS.
Methods: A single-center, prospective trial was performed to compare the reduction in the daily administered dose of antiparkinsonian medications following directional versus omnidirectional bilateral subthalamic DBS in advanced Parkinson's disease.

Results: A total of 37 patients with directional DBS and 37 subjects with omnidirectional DBS were enrolled. Demographic-, disease- and medication-related characteristics at baseline (pre-operative examinations) were identical between the two groups. Demographic, disease-, and medication-related data were reassessed, and all patients underwent detailed neurological and neuropsychological examinations one day, 6 months and 12 months postoperatively. Differences in the change in levodopa equivalent daily dose, the number of patients receiving oral monotherapy and not treated with levodopa after the surgery, and the number of post-operative tablets of the required daily antiparkinsonian medications were compared between the two groups.
Conclusions: Assuming that directional stimulation is more efficient than omnidirectional stimulation, it can be hypothesized that directional stimulation may lead to greater reduction in the total daily administered dose of antiparkinsonian medications. Our findings can be important for future cost-effectiveness calculations.
Disclosure: This study was supported by the ÚNKP-20-4 New National Excellence Program of the Ministry for Innovation and Technology from the Source of the National Research, Development and Innovation Fund and a grant from Abbott Laboratories.

P63
A nationwide study of the incidence, prevalence and mortality of Parkinson's disease in the Norwegian population

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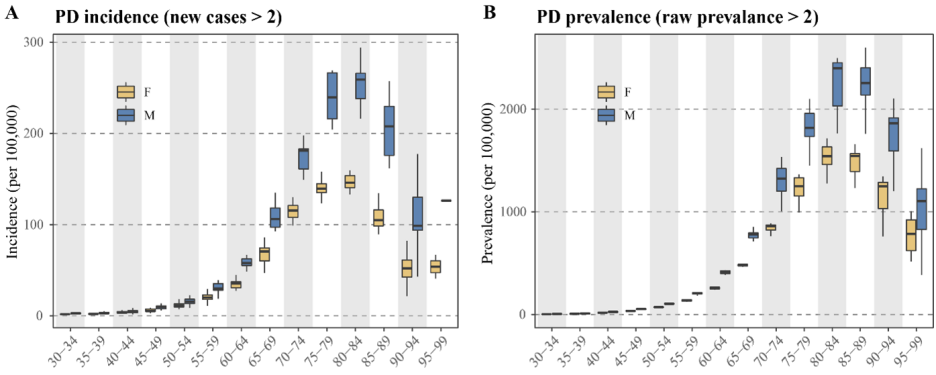
Background: Epidemiological studies of Parkinson's disease (PD) show variable and partially conflicting findings with regard to incidence, prevalence and mortality.
We aimed to determine the nationwide incidence, prevalence and mortality of PD in the Norwegian population compared to the general population.
Methods: We used the Norwegian Prescription Database, a population-based registry of drug prescriptions dispensed from Norwegian pharmacies, to assess the incidence, prevalence and mortality of PD over the period 2004-2017. PD diagnosis was defined by proxy, based on the prescription dopaminergic drugs over a continuous time. In total, 13,053 male- and 10,143 female-PD patients were identified.

Results:



C Incidence

AgeGroup	Estimate_Sex (SE)	pValue_Sex	Estimate_Year (SE)	pValue_Year
30–59	0.36 (0.094)	1.11e−04***	−0.052 (0.014)	1.34e−04***
60–64	0.53 (0.065)	3.50e−16***	−0.028 (0.0094)	2.57e−03**
65–69	0.49 (0.043)	5.89e−30***	−0.022 (0.0061)	1.97e−04***
70–74	0.42 (0.038)	8.65e−29***	−0.0035 (0.0054)	0.51
75–79	0.53 (0.037)	9.19e−47***	0.0039 (0.0052)	0.46
80–84	0.55 (0.04)	1.15e−43***	−0.0035 (0.0058)	0.54
85–89	0.63 (0.057)	5.99e−29***	−0.015 (0.0083)	0.07
90–94	0.71 (0.13)	1.76e−08***	−0.011 (0.018)	0.52
95–99	0.77 (0.42)	0.06	0.02 (0.059)	0.74

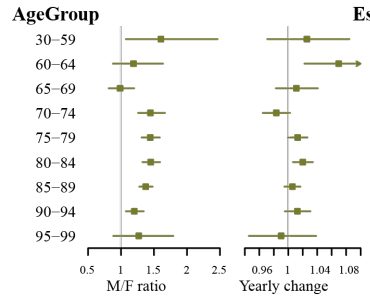
D Prevalence

AgeGroup	Estimate_Sex (SE)	pValue_Sex	Estimate_Year (SE)	pValue_Year
30–59	0.41 (0.097)	2.45e−05***	0.0047 (0.014)	0.74
60–64	0.47 (0.038)	2.01e−34***	0.01 (0.0056)	0.07
65–69	0.47 (0.037)	2.56e−37***	0.0062 (0.0054)	0.25
70–74	0.44 (0.028)	8.93e−54***	0.024 (0.0041)	7.40e−09***
75–79	0.4 (0.019)	5.13e−98***	0.028 (0.0027)	1.92e−24***
80–84	0.4 (0.017)	1.26e−122***	0.03 (0.0024)	4.74e−35***
85–89	0.42 (0.025)	2.02e−63***	0.029 (0.0036)	4.37e−16***
90–94	0.44 (0.043)	4.26e−24***	0.047 (0.0062)	4.93e−14***
95–99	0.36 (0.084)	2.38e−05***	0.062 (0.011)	3.43e−08***

Figure 1; PD incidence and Prevalence

A PD mortality

AgeGroup	Estimate_Sex(SE)	pValue_Sex	Estimate_Year(SE)	pValue_Year
30–59	0.47 (0.21)	0.03	0.026 (0.028)	0.37
60–64	0.17 (0.16)	0.28	0.067 (0.023)	4.01e−03**
65–69	−0.0145 (0.1)	0.88	0.011 (0.015)	0.45
70–74	0.37 (0.073)	4.04e−07***	−0.017 (0.01)	0.09
75–79	0.37 (0.05)	1.70e−13***	0.013 (0.007)	0.06
80–84	0.37 (0.048)	8.10e−15***	0.02 (0.007)	4.40e−03**
85–89	0.32 (0.038)	1.36e−16***	0.0057 (0.0057)	0.32
90–94	0.18 (0.058)	1.69e−03**	0.013 (0.009)	0.16
95–99	0.24 (0.18)	0.19	−9.84e−03 (0.024)	0.68



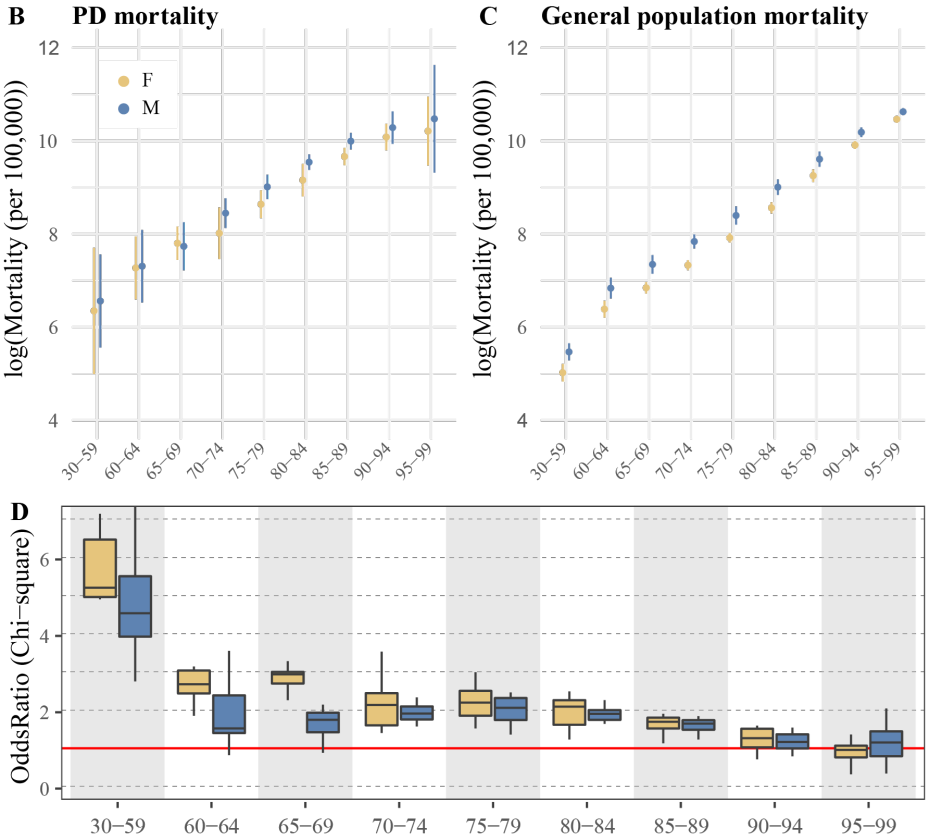
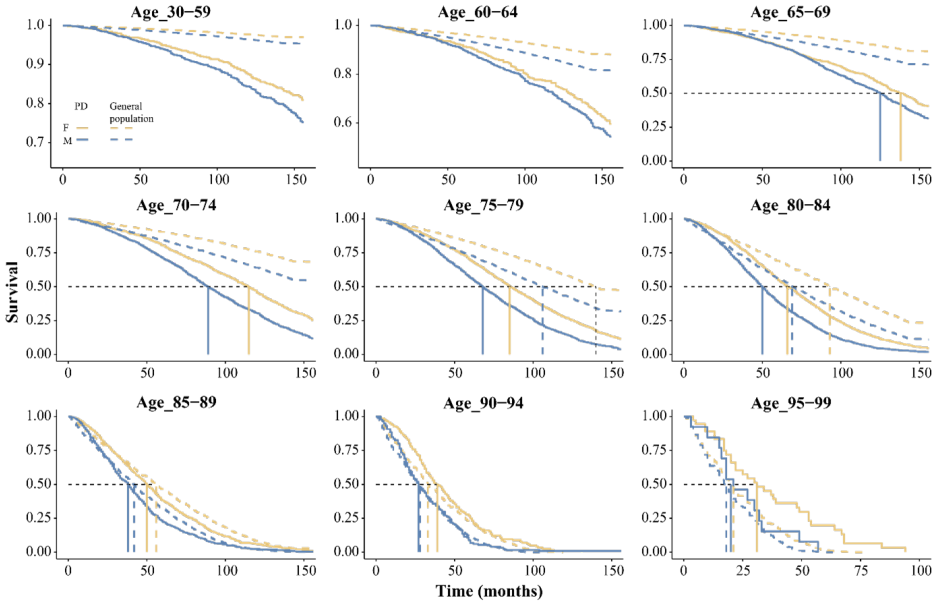


Figure 2; PD mortality ratio Male/Female



Time (month) to 50% survival										
		30-59	60-64	65-69	70-74	75-79	80-84	85-89	90-94	95-99
General population	Male	> 156	> 156	> 156	> 156	106	70	42	28	18
	Female	> 156	> 156	> 156	> 156	140	93	56	33	20
PD	Male	> 156	> 156	125	89	68	50	38	27	21
	Female	> 156	> 156	138	115	85	66	50	39	31

Figure 3; Kaplan-Meyer survival curves for PD according to age

Conclusions: PD epidemiology, including sex-differences, is extremely dynamic and is highly age and time-period dependent. Sex differences in PD mortality are unlikely to stem from disease-specific negative impact of survival in males.

P64
Apomorphine sublingual film for treatment of "OFF" episodes in patients with Parkinson's disease: Effect on MDS-UPDRS part III subdomains

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Background: In a 12-week pivotal study, apomorphine sublingual film (APL) was efficacious and generally well-tolerated for on-demand treatment of "OFF" episodes in patients with Parkinson's disease (PD). Herein, we evaluated effects of APL on MDS-UPDRS Part III subdomains.
Methods: In patients with PD and "OFF" episodes on stable PD medications, titration of APL (10–35 mg; 5-mg increments) occurred during practically defined "OFF" to the dose that resulted in FULL "ON" by 45 minutes. Post hoc analysis evaluated change from predose to 30 minutes postdose in MDS-UPDRS Part III subdomain scores at week 12 in patients randomized to APL or placebo. Association between change in subdomain and total MDS-UPDRS Part III scores was evaluated by Pearson's correlation coefficient.
Results: In 109 patients (APL, n=54; placebo, n=55), predose mean Part III scores were 11.6 (APL) vs 12.3 (placebo) for midline function, 4.5 vs 4.0 for rest tremor, 7.0 vs 7.7 for rigidity, 5.3 vs 5.4 for right upper extremity (RUE) bradykinesia, 5.5 vs 5.8 for left upper extremity (LUE) bradykinesia, 2.5 vs 1.4 for postural and kinetic tremors, and 6.9 vs 7.4 for lower limb bradykinesia.
Mean changes in Part III scores from predose to 30 minutes postdose at week 12 were –2.7 (APL) vs –1.3 (placebo) for midline function (r=0.65 vs 0.73), –1.3 vs –0.6 for rest tremor (r=0.36 vs 0.47), –1.9 vs –0.7 for rigidity (r=0.61 vs 0.88), –1.4 vs –0.3 for RUE bradykinesia (r=0.81 vs 0.76), –0.7 vs –0.4 for LUE bradykinesia (r=0.53 vs 0.71), –1.0 vs –0.1 for postural and kinetic tremors (r=0.19 vs 0.34), and –1.1 vs –0.5 for lower limb bradykinesia (r=0.70 vs 0.78).
Conclusions: On-demand treatment with apomorphine sublingual film for "OFF" episodes improved motor function across all MDS-UPDRS Part III subdomains vs placebo, with the greatest effect on midline function.

P65
Recruitment for decentralized studies in Parkinson's disease

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Background: Traditional in-person research studies are often slow to recruit and burdensome for participants. The ongoing COVID-19 pandemic has interrupted Parkinson's disease (PD) clinical research. To assess the feasibility of enrolling participants with a decentralized research model, we compared recruitment outcomes across three decentralized, single-site studies.
Methods: In three decentralized observational studies of PD—FIVE, a cross-sectional study of Fox Insight participants with and without PD (n=203); VALOR-PD, a 36-month longitudinal study of 23andMe-identified carriers of *LRRK2* G2019S with and without PD (n=277); and AT-HOME PD, a 24-month study of former phase III clinical trial participants (n=226)—we examined the number of participants recruited, speed of recruitment, geographic distribution of participants, and recruitment-enhancing strategies.
Results: The mean rate of enrollment per study ranged from 3.7-6.4 participants per week over a period of 32 to 61 weeks (Table 1).

	FIVE	VALOR-PD	AT-HOME PD
Participants invited, n	2,125	3,808	505
Consented to contact and pre-screened, n (%)	256 (12.0%)	336 (8.8%)	348 (68.9%)
Consented to study, n (%)	223 (10.5%)	293 (7.7%)	240 (47.5%)
Completed baseline visit, n (% of target enrollment)	203 (101.5%)	277 (92.3%)	226 (44.8%)
Weeks to complete enrollment, n	32	60	61

Table 1.

The 706 participants spanned 42 U.S. states and were demographically homogenous in regards to race (>95% white) and level of education (>88% with more than a high school education). The percentage of participants living in primary care Health Professional Shortage Areas in each study ranged from 30.3-42.9%. Enrollment rates were better when initial contact was from a familiar source and improved with implementation of a multimodal approach and use of materials tailored to target specific.

Conclusions: Recruitment of geographically dispersed virtual cohorts by a single site is fast and feasible. Our experience may inform recruitment practices for increasingly important and desired decentralized clinical studies.

P66
Inhaled levodopa as a treatment for Parkinson's disease (PD) patients in an emergency setting

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Background: OFF phenomena in patients with advanced PD, occasionally present as severe fluctuations of motor and non-motor symptoms leading to emergency department (ED) visits and extensive workups. Oral carbidopa/levodopa has limited utility treating patients with severe OFF-period akinesia involving oropharyngeal muscles and impaired swallowing, and gastroparesis can lead to delayed levodopa absorption.

Methods: We report use of CVT-301 (inhaled levodopa) in treating a series of PD patients with complicated OFF periods.

Results: *Case 1:* An 81-year-old male with dementia attending our clinic for a follow-up visit, was found to have a complicated OFF episode with severe hyperpyrexia, drenching sweat, severe hypertension (BP205/170), sinus tachycardia (HR125), dyspnea (RR22), freezing and rigidity in all extremities, tremor, and severe confusion.

Last dose of levodopa was >5hrs prior to examination. CVT-301 was administrated, leading to stabilization of vital signs (BP 155/95, HR95, RR18) and improvement of gait, tremor, and rigidity within 10min.

Case 2: 70-year-old patient with advanced PD on carbidopa/levodopa intestinal gel (LCIG) presented to ED with altered mental status, respiratory distress, autonomic instability, and severe rigidity, BP185/110, HR120, RR25, O_2 sats 90%. Patient was in a severe OFF episode due to LCIG tube failure. He was successfully treated within 15min of CVT-301 administration in ED. Vital signs stabilized and respiratory distress resolved. Patient was discharged <24hrs after PEG tube replacement and resumed LCIG treatment.

Case 3: 78-year-old male, post deep brain stimulation (DBS) and on extended-release carbidopa/levodopa, presented to ED in an OFF period with no response to routine carbidopa/levodopa dose due to gastroparesis. CVT-301 dose rapidly improved motor symptoms. Neurology consultation revealed patient had accidentally turned off DBS leading to severe OFF period. After resuming DBS, patient was successfully discharged.
Conclusions: CVT-301 administration in patients with complicated OFF episodes rapidly improved their OFF symptoms, prevented hospital admission and unnecessary and costly acute workup in the emergency setting.

P67
CVT-301 (levodopa inhalation powder): Meta-analysis of safety in patients with Parkinson's disease (PD)

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Background: CVT-301 (Inbrija®) is approved for the treatment of OFF episodes in PD patients on an oral carbidopa/levodopa regimen. In a phase 3, double-blind study, CVT-301 84mg improved motor function in PD patients with OFF periods within 30 minutes as measured at 12 weeks by change in Unified Parkinson's Disease Rating Scale Part III scores. More patients achieved and maintained an ON state within 60 minutes postdose vs placebo. CVT-301 was generally well tolerated.
Safety results from this study were combined with results from a 4-week, phase 2b, double-blind, placebo-controlled study and a 12-month safety study of CVT-301 compared to an observational cohort (OC) control.
Methods: Patients were receiving oral dopa-decarboxylase inhibitor/levodopa, experiencing ≥2 hours/day of OFF periods and randomized to CVT-301 (60mg or 84mg; only the 84mg is included in this analysis) or placebo or OC (no study drug administered), to be taken up to 5 times/day when subjects experienced return of OFF symptoms. Safety measurements included treatment-emergent adverse events (TEAEs), and serious AEs (SAEs) and monitoring special-interest AEs. Risk differences (RD) were compared between treatments by meta-analysis.
Results: The combined safety population was 709 patients. Combined study TEAEs were higher in CVT-301, but were not significantly different vs placebo or OC (RD 0.074, 95%CI -0.058, 0.206). SAEs and AEs leading to discontinuation showed no significant difference between groups (RD 0.003, 95%CI -0.031,0.038 [SAE]; RD 0.031, 95%CI -0.035,0.098 [discontinuation]). Severe and drug-related TEAEs were higher in the CVT-301 group, but differences were not sig-

nificant (RD 0.021, 95%CI -0.027,0.069 [severe]; 0.185 95%CI -0.038,0.409 [drug-related]). Respiratory system AEs were higher in CVT-301, but not significant (RD 0.073, 95%CI -0.065,0.211). Additional data will be presented.

Conclusions: Overall, TEAEs, SAEs and AEs leading to discontinuation were not significantly different in frequency between CVT-301 and placebo/OC groups, demonstrating that CVT-301 is generally safe and well tolerated.

P68
CVT-301 (levodopa inhalation powder) improves Patient Global Impression of Change (PGIC) over 1 year in patients with Parkinson's disease (PD): A meta-analysis

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Background: CVT-301(Inbrija®) is approved for treatment of OFF episodes in PD patients on oral carbidopa/levodopa. In the phase 3, placebo-controlled, double-blind study, CVT-301 improved motor function in patients experiencing OFF periods at week 12, measured by lower Unified Parkinson Disease Rating Scale Part III(UPDRS-III) scores at 30 minutes postdose. 58% achieved and maintained an ON state<60 minutes postdose vs 36% on placebo. 71.4% of patients on CVT-301 reported improvement in PGIC vs 46.4% on placebo. In a 12-month, open-label extension study, 66.7%-91.9% patients reported PGIC improvement. Also, in a 12-month, open-label, observational control(OC) safety study >75% reported improvement at 3,6, and 12 months.

Methods: PGIC results from the double blind and open-label studies of CVT-301 were combined. Patients on oral dopa-decarboxylase inhibitor/levodopa, experiencing≥2 hours/day of OFF were randomized to CVT-301(60mg/84mg) or placebo or OC (no study drug administered), to be taken ≤5 times/day on return of OFF symptoms.

Results: Pooled results(84mg) show that the proportion of patients taking CVT-301 in controlled and open-label studies who reported PGIC improvement("a little improved,"improved","much improved") ranged from 64.5%-88.6% from 4-52 weeks, respectively.

Of those reporting any improvement, patients with "improved" and "much improved" increased from 29.5% at week 4 to 51.3% at week 36 and 43.2% at week 52. Additional meta-analyses will be presented.

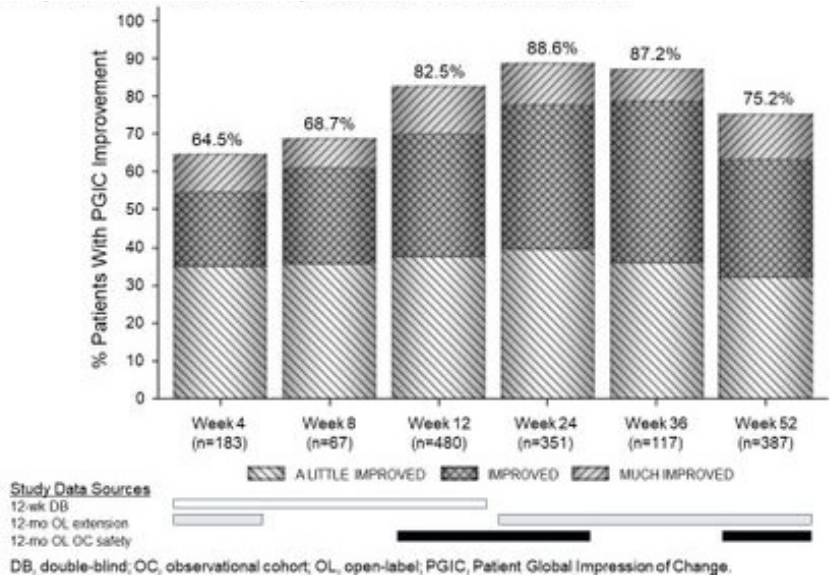

Figure. Proportion of patients with improved PGIC from pooled studies

Conclusions: Proportion of patients on CVT-301(84mg) reporting improvement in their PD on the PGIC increased over the study periods of 4-52 weeks. PGIC improvement, in addition to improvements measured by UPDRS-III support the efficacy of CVT-301 in PD.

P69
Incidence of serotonin syndrome in Parkinson's disease polymedicated patients

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Background: Serotonin syndrome (SS) is a life-threatening condition caused by drugs that affect serotonin metabolism or act as agonists for serotonine receptors. The drugs whose association described (SSRIs and iMAO-B) are frequently used in Parkinson's disease patients
Methods: An observational study was carried out in which a total of 124 patients diagnosed with Parkinson's disease under treatment with iMAO-B were included. The characteristic symptoms of serotonin syndrome, the prescribed drugs were collected from the medical records

Results: The association between the different antiparkinsonian and antidepressant drugs with the development of SS was analyzed through the Chi square test and Fisher's exact test, as well as their value as independent risk factors using a binary logistic regression. An incidence of SS of 32.6% was observed. In a homogeneous sample regarding age and sex, 58.7% required antidepressant treatment, after the establishment of which 17.4% developed Serotonin Syndrome, while 15.2% did so after the introduction of iMAO-B. The type of antidepressant treatment proved to be a determining factor since the risk conferred to SNRIs was higher (OR: 6.09)

The risk of developing Syndrome Serotonergic is minimally superior with AD compared to MAOIs (rasagiline or selegiline) in isolation. There were no differences between the different sexes and ages, nor with the use of dopamine agonists or type of MAO-B inhibitors.

Levo-dopa was not associated with increased susceptibility to developing serotonin syndrome.

In the study, serotonergic syndromes were classified into categories based on their severity, the majority being of the mild type.

Conclusions: This study encourages on SS screening in patients under treatment with MAOI and SSRI as it´s a combination that may lead to the development of a serious condition that can go unnoticed and be confused with banal alterations.

Knowing the incidence of SS will facilitate it´s prevention, diagnostic suspicion and correct approach.

P70
Neuropathological findings of Parkinson's disease with fatal acute gastric dilatation

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Background: Parkinson's disease (PD) is a neurodegenerative disorder neuropathologically characterized by Lewy bodies. Acute gastric dilatation due to severe gastroparesis rarely occurs in PD patients and may cause death. The aim of this study is to investigate neurodegeneration of PD with acute gastric dilatation.

Methods: A 78-year-old man presented with resting tremor involving the left upper limb. Based on the beneficial effect of levodopa, he was diagnosed with PD. He was admitted to our hospital because of aspiration pneumonia at the age of 86 years. After treatment for aspiration pneumonia, he presented acute gastric dilatation. Despite the treatment, he developed

gastric ulcer bleeding and aspiration pneumonitis, leading to multi-organ failure and death. A postmortem examination and alpha-synuclein immunostaining for central nerve and enteric nerve systems was performed.

Results: Severe neuronal degeneration was observed in the dorsal motor nucleus of vagus (DMNV), locus coeruleus, and substantia nigra. Immunohistochemistry with alpha-synuclein antibody (pSyn #64, FUJIFILM WAKO, Osaka, Japan) revealed numerous alpha-synuclein-positive inclusions in the brainstem, limbic regions, neocortex, olfactory bulb, and sympathetic ganglion, corresponding to stage IV Lewy body disease according to the Unified Staging System for Lewy Body Disease.

Immunohistochemical analysis with the alpha-synuclein antibody showed alpha-synuclein-positive deposits in the plexus of the esophagus, stomach, small intestine, and colon.

Conclusions: Injection of 6-hydroxydopamine (6-OHDA) into the central nervous system induces neurochemical changes in the DMNV and reduced the number of ChAT immunoreactive neurons in gastric tissues.

These results revealed that neurochemical changes and degeneration in the DMNV, vagus nerve and enteric nervous system may be associated with nigrostriatal degeneration, which ultimately leads to gastric hypomotility.

The pathological findings of our case demonstrated neurodegeneration in all nervous systems associated with gastric motility. Clinically, physicians should keep in mind that acute gastric dilatation is a fatal complication in PD.

P71
Phenotypic changes in peripheral blood T-lymphocytes in patients with Parkinson's disease

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Background: Parkinson's disease (PD) is one of the most common neurodegenerative diseases. In recent years, there is growing evidence that the pathogenesis of this disease is connected with and peripheral immune processes. Cytomegalovirus infection can increase the expression of CD57 molecule also CMV stimulates replicative senescence of T-cells. This study aimed to analyze the expression of CD57 by peripheral T-lymphocytes of PD patients and determining the effect of CMV on immunosenescent.

Methods: We examined 31 PD patients, 33 healthy elderly donors (OHD), and 30 young healthy donors (YHD). Immunophenotyping was performed using flow cytometry. Serotyping of donors for CMV was performed by ELISA.

Results: The proportion of T-lymphocytes ($CD3^+CD56^-$) expressing the CD57 marker was lower in the PD group than in the OHD group (8.7 and 13.1, p = 0.02). At the same time, the proportion of these cells in the group of the YHD was significantly lower than in the group of PD and OHD. 76% of the OHD, 73% of the YHD, and 100% of PD patients were seropositive for CMV IgG. To exclude the influence of CMV on the level of CD57 expression, a comparison was made only between the groups of donors infected with CMV.
No differences were found in the expression of the CD57 molecule by T-lymphocytes in the PD and the YHD groups (8.57 and 6.8 p = 0.2), while significant differences were revealed between the OHD and YHD groups (14.4 and 6.8 p = 0.0001).
Conclusions: This study demonstrates that the peripheral immune profile in PD is not typical for older donors. We found that there is no replicative senescence of T-cells. Besides, we observe the absence of CMV infection-induced T cell aging in PD patients.
Acknowledgments: The reported study was funded by RFBR, project number 20-315-90072.

P72
Characteristics of COVID-19 in a cohort of individuals with Parkinson's disease

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Background: The novel coronavirus disease (COVID-19) is a pandemic with significant health concerns for patients with underlying medical conditions. Individuals with Parkinson's disease (PD) are vulnerable and may be more susceptible to severe illness and poor outcomes with COVID-19. We describe the clinical characteristics of 12 patients with PD and COVID-19.
Methods: We retrospectively analyzed data from 12 consecutive patients with PD and COVID-19 presenting to a suburban hospital in Washington State, USA.
Results: The majority of our sample was male (58%) with a median age of 72 years. The most common presenting symptoms of COVID-19 were cough (75%), fever (67%), and shortness of breath (58%). The most common comorbid conditions were hypertension (58%), cardiovascular disease (50%), diabetes mellitus (25%), COPD (17%), asthma (8%), and chronic kidney disease (8%).
One patient had a history of deep brain stimulation and was discharged on baseline PD medications. Two patients were asymptomatic with one testing positive on routine screening following an outbreak at her residential facility and the other testing positive prior to nocturnal

polysomnogram and received monoclonal antibody infusion as part of FDA emergency use authorization. Six patients (50%) required hospital admission. Three of the four patients with PD dementia presented with metabolic encephalopathy out of which two died. Two patients (17%) presented with worsening of PD tremor, one patient (8%) presented with worsening lightheadedness, and one additional patient (8%) with increased falls.

Conclusions: In this cohort of patients with PD and COVID-19, 58% experienced worsening of underlying PD including tremor, lightheadedness, and falls. In the four patients with PD dementia, COVID-19 resulted in metabolic encephalopathy in three and death in two. Thus, PD dementia represented the strongest risk factor for severe illness and poor outcome.

The results of our study will be helpful to inform those with PD, care partners, and treating physicians.

P73
Apomorphine sublingual film for "OFF" episodes in patients with Parkinson's disease: Impact of concomitant antiemetics/dopamine agonists on nausea/vomiting

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Background: In a 12-week pivotal study, apomorphine sublingual film (APL) was efficacious and generally well-tolerated for on-demand treatment of "OFF" episodes in patients with Parkinson's disease (PD). Herein, we analyzed effects of concomitant antiemetics and dopamine agonists (DA) on nausea and vomiting in patients receiving APL.

Methods: In a long-term safety (LTS) study (NCT02542696) of patients with PD and "OFF" episodes on stable PD medications, APL dose titration (DT; 10–35 mg; 5-mg increments) occurred during practically defined "OFF" to a dose resulting in FULL "ON" within 45 minutes. In the LTS phase, patients self-administered APL for ≤5 "OFF" episodes/day. Antiemetics were permitted for those experiencing nausea/vomiting. Interim results of nausea/vomiting TEAEs during both phases are reported descriptively.

Results: In the DT and LTS phases, 425 and 345 patients, respectively, received ≥1 APL dose. In the DT phase, nausea, vomiting, and nausea leading to discontinuation were similar for antiemetics vs no antiemetics; vomiting leading to discontinuation was not observed. In the LTS phase, nausea, vomiting, and vomiting leading to discontinuation were similar; nausea lead-

ing to discontinuation was higher. In the DT phase, nausea, vomiting, and nausea leading to discontinuation were lower for DA vs no DA. In the LTS phase, nausea, vomiting, and nausea leading to discontinuation were lower; vomiting leading to discontinuation was similar.

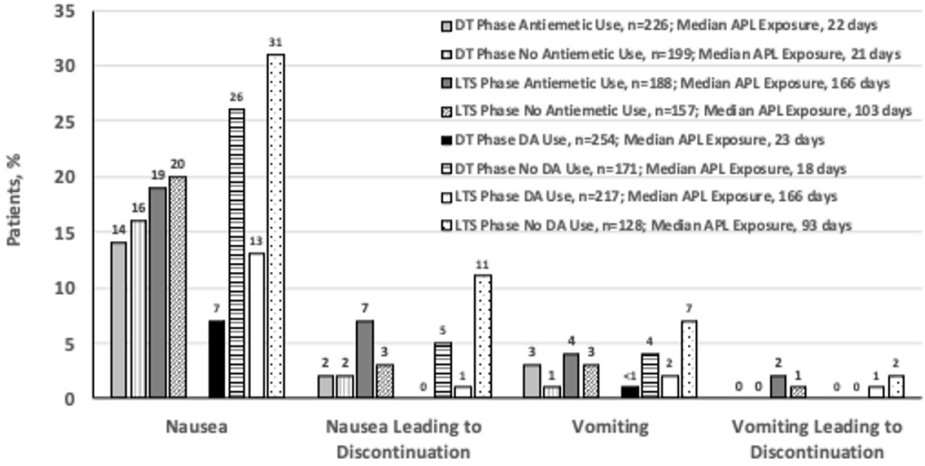

Figure: Nausea and Vomiting by Antiemetic or DA Use

Conclusions: Interim data suggest that patients using apomorphine sublingual film may not require antiemetics, and patients using other DAs (vs no DAs) had lower incidence of nausea/vomiting TEAEs.

P74
Sustained pill burden reduction among Medicare fee-for-servicepatients with Advanced Parkinson's Disease (APD) after initiation of Carbidopa/Levodopa Enteral Suspension

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Background: APD patients often require complex polypharmacy regimens to manage motor fluctuations, which results in significant pill burden. Erratic gastric emptying, along with sub-optimal adherence, further challenge the ability of orals alone to provide consistent symptom control. This study evaluates the real-world comparative impact of CLES initiation on pill burden reduction in APD patients.

Methods: Medical and pharmacy claims from 100% Medicare FFS 2015-2018 data were used. Specialty pharmacy data linkage was used to identify CLES-patients and controls. Index date was defined as the first CLES shipment date and enrollment date for CLES-patients and controls, respectively. Only patients with minimum continuous enrollment of 6 months pre-index (baseline) and 2-year post-index (follow-up) were included in the analysis. Pill burden was defined as total number of PD-related pills/day, measured as 30-day averages/month in the baseline and follow-up period. Pill burden was also calculated for baseline (6 months pre-index), short-term (0-6 months post-index), and long-term (7-12 months post-index). Treatment effect (i.e., reducing pill burden) was evaluated based on unadjusted (Mann-Whitney U tests) and adjusted (generalized linear models adjusted for age, gender, region, comorbidities, and dual coverage) differences between CLES-patients and controls.

Results: At baseline, the CLES-patients (n=244) and controls (n=190) had comparable age (mean: 71$\pm$8 and 72$\pm$9, respectively; p-value>0.05) but CLES-patients had higher pill burden (mean: 12±6 and 10±5, respectively; p-value<0.001). Compared to baseline, treatment effect in CLES-patients was significantly higher than controls in the short- and long-term ($\Delta_{Unadjusted}$: -7.0, $\Delta_{Unadjusted}$: -9.0; p-value<0.0001). Adjusted estimates suggest that CLES-patients take 52% and 57% fewer pills per day than controls during 0-6 and 7-12 months post-index, respectively (p-value<0.0001).

Conclusions: This study demonstrates a significant immediate and sustained reduction in pill burden over 12-months after CLES initiation in APD patients. The impact of no change in the pill burden in the control group needs to be further evaluated.

P75
Cerebral vascular lesions in Parkinson's disease patients. Preliminary results of Moldovan PD cohort study

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Background: Associated cerebral vascular lesions **(**CvaLs) are frequent and confers greater severity to PD. Study objective - determining association and impact of CVaLs on PD in Moldovan cohort (part of national project 20.80009.8007.39)
Methods: These are preliminary data of 111 consecutive PDp from a national tertiary center, mean age 64.87 ± 7.69 y.o., mean disease duration 50.21 ± 38.61 months, 48 women (43.2%) and 63 (56.8%) men. Clinical evaluation and brain MRI 3T were performed. Presence of: white matter lesions, lacunas, deepening of cerebral fissures, widening of the ventricles and of the perivascular spaces was visually rated. Volumetry of CVaLs - in process.
Results: CVaLs were found in 78.4% of all cases; in 75.3% of definite and 77% of probable PDp; also in 90% cases of predominantly lower body parkinsonism.
Normal cognition patients had CVaLs in 83%, MCI patients – 76.5%, mild dementia patients – 75.0%, and moderate dementia patients – 100% of cases (there were no severely demented patients so far).
Patients with CVaLs exhibited a significantly higher: number of vascular risk factors (2.83 ± 1.38 vs. 1.73 ± 1.19, p = 0.013), QRISK3 scores (19.68 ± 16.15 vs. 12.9 ± 6.58, p = 0.015), relative risk (5.48 ± 13.45 vs. 1.70 ± 0.39, p = 0.009), and levodopa equivalent daily dose (639.98 ± 223.04 vs. 439.69 ± 224.87, p = 0.048).
The UPDRS scores ($UPDRS_{off}$ 47.26 ± 13.21 vs. 44.13 vs. 8.20; $UPDRS_{on}$ 35.49 ± 11.8 vs. 29.89 vs. 8.99) and Beck scores (7.26 ± 5.62 vs. 6.86 vs. 4.37) were higher; and MoCA scores (21.93 ± 4.25 vs. 22.38 vs. 4.56) lower than in control, thus not reaching the statistical significance.
Conclusions: Patients with PD and CVaLs have more cardiovascular risk factors, thus a higher QRISK3 scores and relative risk. They are more severely affected and require higher doses of dopaminergic drugs; have more depression and cognitive impairment.

P76
Non-permitted Food colorants induced neurotoxicity in corpus striatum of rats

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Background: Non-permitted Food colorants (NPFCs) caused several toxicities, thus make it subject to regulation by different regulatory and monitoring organizations like FDA, EFSA, etc. Evidence suggested that injudicious use of most of the synthetic NPFCs is associated with adverse health effects in humans and animals.
The present study was focused to investigate the effects of NPFCs (metanil yellow-MY, malachite green-MG and sudan III-SIII) on oxidative stress, mitochondrial complex activity, and neuroenzyme activity in the corpus striatum of rats.
Methods: Rats were divided into 5 groups and treated with MY (430 mg/kg), MG (13.75 mg/kg), SIII (250 mg/kg), mixture (YGR) (MY 143.33 + MG 4.52 + SIII 83.33 mg/kg) and 1 % gum acacia serve as control p.o. for 60 days. Rats were decapitated for brain region isolation and processed for biochemical and neurochemical analysis through valid standard protocols.
Results: The treatment group shows significant increase in lipid peroxidation and decreased level of reduced glutathione, superoxide dismutase and catalase activity in corpus striatum of rats as compared to controls. A significant decrease in the activity mitochondrial complex I and II, acetylcholinesterase and monoamine oxidase-B activity were also observed in NPFCs treated groups as compared to controls.
Conclusions: The results of the present study demonstrated that chronic exposure to NPFCs causes alteration in antioxidant defense mechanism, mitochondrial dysfunction, and cholinergic and dopaminergic dysfunctions in the corpus striatum of rats, which could be further associated with impaired motor dysfunction and pathological alterations like neurodegenerative diseases.

Other Parkinsonian Disorders

P77
Does neutrophil-lymphocyte ratio predict short survival in multiple system atrophy?

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Background: Neutrophil to lymphocyte ratio (NLR) is an inexpensive and easily applicable marker that indicates the peripheral inflammation, which can predict prognosis of neurodegenerative diseases. However, there have been no researches focusing on the relationship between NLR and prognosis in multiple system atrophy (MSA). We aimed to explore the prognostic significance of NLR in MSA.
Methods: The current study enrolled 169 MSA patients and 163 matched healthy controls (HC). According to the tertile of NLR, MSA patients were divided into three groups. Kaplan-Meier survival analysis and the Cox regression model were performed to assess the effect of NLR on survival.
Results: When compared to HC, MSA patients had higher level of NLR (2.17±0.92 vs 1.85±0.70, P=0.001). There were 67 (39.6%) MSA patients died and 102 (60.4%) MSA patients still alive at the end of follow up. The survival time of MSA patients in group 3 was shortest than the other two groups (P=0.013).
In the multivariable Cox regression model, higher level of NLR increased the risk of mortality in MSA patients after adjusting for age, sex, subtype, onset symptom, BMI, disease duration, total UMSARS score, OH, and urinary incontinence. (HR=1.922, 95% CI 1.046-3.531, P=0.035). In addition, higher level of NLR increased the risk of mortality in MSA-C patients (HR=2.398, P=0.033) and in male MSA patients (HR=3.483, P=0.027).
Conclusions: MSA patients had a higher level of NLR compared with HC. In addition, High level of NLR was significantly associated with poor survival in MSA, especially in MSA-C subtype and male patients.

P78
Biopsychosocial aspect of patients with X-Linked Dystonia Parkinsonism: Its implications on quality of life

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Background: This study aims to describe the demographic profile in terms of age, marital status, annual family income, and educational attainment; to describe the physical, psychological, and social manifestations; to determine and describe coping mechanisms; to determine the goals, aspirations, and needs; and, to determine the interaction and impact of the lived experiences to the quality of life of XDP (X-Linked Dystonia-Parkinsonism) patients.
Methods: This qualitative-phenomenological study was conducted in the island of Panay. Purposive sampling was utilized. The researchers utilized in-depth interview, observation, and triangulation as part of the data collection methods. The data was transcribed verbatim, kept for content analysis, and coded in their appropriate cell categories after themes were identified.
Results: Ten male patients who were residents of Panay, aged 30-65 years old participated in this study. Disease manifestations included limb dystonia, blepharospasm, truncal torsion, oromandibular symptoms, torticollis and dysphonia, contributing to limitations to performing activities of daily living. Denial was the most common initial reaction after being diagnosed with XDP. Social manifestations were greatly affected by family and community. Money and medications were the primary needs identified by the patients with hopes of a better future for their families. There was an overall deterioration in the quality of life of the patients.
Conclusions: XDP patients had individualized experiences with the disease. The patient's quality of life was affected by different interlocking chain of factors. The multidimensional aspects of the quality of life should be placed under constant check and balance; the family and health workers alike should be the accountants.
Finding meaning to their quality of life did not only rely on physical relief of symptoms, but in gaining social acceptance, independence, and life-long support and love.

P79
The Implications of Upper Motor Neuron Burden in Multiple System Atrophy

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Background: The diagnosis of multiple system atrophy (MSA) is based on four clinical domains: autonomic, parkinsonism, cerebellar, and corticospinal tract symptoms and signs. However, the involvement of corticospinal tract, manifesting as upper motor neuron (UMN) symptoms, is frequent yet poorly understood in MSA.
We conducted the present study to investigate if the UMN symptoms and signs in MSA is associated with other characteristic features.
Methods: We reviewed 40 autopsy-confirmed MSA cases from New York Brain Bank and assessed the UMN signs. The overall UMN burden score was 0-36, calculated by scoring deep tendon reflexes, muscle tone, and pyramidal signs. MSA patients were divided into those with high UMN burden (HUMN) ≥ 18 and low UMN < 18 (LUMN). We compared the clinical characteristics of MSA patients with HUMN vs. LUMN using Chi-Square and independent t test. We investigated if UMN burden is associated with the presence of autonomic, parkinsonism, and cerebellar features. We conducted a multivariable linear regression to examine if UMN burden is associated with survival.
Results: MSA cases with HUMN (35%, n = 14) and those with LUMN (65%, n = 26) have similar age, sex, age of onset, and disease duration. MSA cases with HUMN are more likely to be MSA-P than those with LUMN ($p = 0.016$). MSA patients with HUMN are more likely to have urinary incontinence (OR = 4.00, $p = 0.046$), but less likely to have orthostatic hypotension (OR = 0.24, $p = 0.043$) and erectile dysfunction (OR = 0.03, $p = 0.006$). The HUMN subjects do not differ from LUMN in regards to bowel dysfunction, stridor, and dry eyes. Patients with HUMN and those with LUMN are not different in survival.
Conclusions: UMN symptoms are associated with different MSA subtypes and autonomic features. Further studies are needed to fully characterize this often-neglected clinical domain for MSA.

P80
Levetiracetam for sleep disorders in Huntington's disease: A case report

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Background: A common co-morbidity of Huntington's Disease (HD) is sleep disorders. Numerous treatment modalities have been suggested to provide relief to this patient population. We present the case of a HD patient who was tried on Levetiracetam to help treat his superimposed sleep disorder.
Methods: To assess if Levetiracetam was useful in preventing insomnia, we used the Pittsburgh Insomnia Rating Scale (PIRS) to obtain a quantitative value for his sleep disturbances.
Results: Patient A is a 50 -year old male who was diagnosed with HD in 2011.
Since 2017, he has had increasing insomnia, which is described as an inability to fall back asleep if awakened in the middle of the night. He was started on 125 mg of Levetiracetam as needed for insomnia with instructions to take another 125 mg one hour later if there is no effect in April 2019. The patient followed this regimen for two weeks with minimal improvement and was instructed to increase the dosage to 250 mg nightly as needed.
A few weeks later, the patient's insomnia continued. The patient was increased to 500 mg of Levetiracetam before bedtime, followed by another 500 mg if he was still awake 2 hours later.
The patient was concurrently taking Paroxetine, Clonazepam, and Trazadone, but they were prescribed for increasing anxiety. The Trazadone was held because the patient was sleeping through periods of urinary incontinence. A before and after PIRS showed a difference of 38 points for the total score.
Conclusions: Patient A showed promising results while on Levetiracetam. Although he was on other sedative inducing medications concurrently, his insomnia was best treated once Levetiracetam was started at 500 mg.
A prospective study on a larger HD patient population is necessary to assess Levetiracetam's efficacy as a treatment for HD patients' sleep disorders.

P81
SNCA differential expression in different brain regions in isolated REM sleep behavior disorder

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Background: To identify genes expression association in isolated REM sleep behavior disorder (iRBD), we performed a transcriptomic wide association study (TWAS).
Methods: Two summary statistics datasets of RBD genome-wide association studies (GWAS) were obtained. The first GWAS consisted of 1,061 iRBD patients and 8,386 controls of European ancestry. Then, a meta-analysis of 2,843 European iRBD and Parkinson's disease (PD) patients with probable RBD along with 139,636 controls was performed.
We also obtained the 2019 PD GWAS summary statistics to compare TWAS results. The relevant brain tissue panels from GTEx were downloaded from the FUSION, PrediXcan, and PTWAS website. To perform transcriptomic imputation, FUSION, PrediXcan, and PTWAS were used to

predict the gene expression values in 13 brain tissues. We used default settings along with recommended weights and reference panels for each method. Candidate genes were nominated by at least two different TWAS methods.

Results: The top candidate gene in our analysis was *SNCA*. This gene had high concordance across the different TWAS methods. Interestingly, *SNCA* was detected to be significantly associated with expression in some tissues such as the cortex (zscore (z) = 7.98; $p = 1.49*10^{-15}$), cerebellar hemisphere (z = 6.38; $p = 1.80*10^{-10}$), but not in the substantia nigra ($p = 0.011$). The PD top GWAS SNP was not associated with *SNCA* expression in the cortex nor the substantia nigra.

Conclusions: In this study, we performed an iRBD TWAS using different methods in several brain tissues. When examining iRBD and meta-analysis of iRBD, *SNCA* was associated with expression changes in multiple brain regions but not in the substantia nigra. Interestingly, the top *SNCA* PD GWAS SNP has different expression profile. This could suggest that *SNCA* expression could play a different role in iRBD than PD. Further analysis with a larger cohort in the future will be needed.

Dystonia

P82
A case of severe cervical dystonia after radiofrequency ablation

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Background: Severe cervical dystonia that has exhausted all medicinal and rehabilitation treatment options sometimes seeks end of the line treatment with surgical options, such as Deep Brain Stimulation (DBS), or RFA ramectomy/peripheral denervation.
The significance of this case report is in regard to the timeline of our patient undergoing RFA ramectomy for neck/arm pain two days prior to the development of her cervical dystonia. Her development of dystonia after undergoing a potential treatment option, is confounding.
Methods: A chart review in EPIC Electronic Medical Record (EMR), live interview and examination, as well as a video recording were performed to gain pertinent information regarding this patient's history and pathology. A review of literature was also performed to further assess etiology/causation of her cervical dystonia using UNMC's library as well as the PubMed literature database.
Results: A 56-year-old female presented to the neurology office for evaluation of severe cervical dystonia. She had chronic left arm pain and paresthesia for which she had tried and failed multiple treatments. Six months prior to presentation, she underwent RFA at levels C2 through C5 for the left arm pain, during which she had no complications. Two days after RFA, she woke with excruciating pain on the right side of her head and neck with her head severely bent to the right and her chin to her chest. She has tried eight different interventions without any improvement in her head position.
Conclusions: We believe the etiology of her dystonia to be due to peripheral nerve injury from RFA. Acute dystonic reaction, tardive, and functional dystonia were ruled out due to her being on a stable dose of her antipsychotic months prior to RFA and after, the persistence of symptoms, the severe degree of hypertrophy in selected cervical muscle groups, and lack of distractibility.

Chorea, Athetosis, Ballism, Tics

P83
Proof-of-concept study testing SOM3355 (bevantolol) as VMAT2 inhibitor to treat chorea symptoms in Huntington's disease (HD)

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Background: SOM3355 (bevantolol hydrochloride), a β1-adrenoceptor antagonist antihypertensive, was identified by artificial intelligence screening and confirmed by *in vitro* functional studies as a Vesicular Monoamine Transporter type 2 (VMAT2) inhibitor that could be repositioned to treat dyskinetic movements in Huntington's disease (HD). A phase IIa proof-of-concept study was conducted to assess whether SOM3355 reduces chorea in HD patients.
Methods: A double-blind, randomized, cross-over, placebo-controlled study was conducted in 32 HD patients, who were randomly assigned to two arms of 4 sequential 6-week dose periods, testing in cross-over placebo and active drug SOM3355 at 100 and 200 mg BID.
The primary endpoint was defined as an improvement in the Total Maximal Chorea (TMC) subscore of the Unified Huntington's Disease Rating Scale (UHDRS) in any active drug period of at least 2 points compared with placebo period.
Results: More than half of the patients (57.1%) had an improvement in the TMC score of at least 2 points compared to placebo in any period with SOM3355, thus reaching the primary endpoint. Even more clinically significant TMC improvements of at least 3, 4, 5, and 6 points compared to placebo were seen with SOM3355 in 28.6%, 25.0%, 17.9%, and 10.7% of the patients, respectively.
A mixed model analysis comparing the different periods showed a significant improvement in the TMC score with 200 mg BID compared to placebo ($p=0.0224$), which was confirmed in ratings of Clinical Global Impression of Change (CGIC) and Patient Global Impression of Change (PGIC). Mild elevations in plasma prolactin levels were recorded ($p<0.005$), consistent with the

profile of VMAT2 inhibition. SOM3355 was well tolerated with only mild or moderate adverse events, most of them expected due to the β1-adrenoceptor antagonist effects on the cardiovascular system.
Conclusions: This study confirms that SOM3355 reduces chorea in HD patients with a good safety profile.

P84
Risk factors and prognosis of adult-onset post-pump chorea

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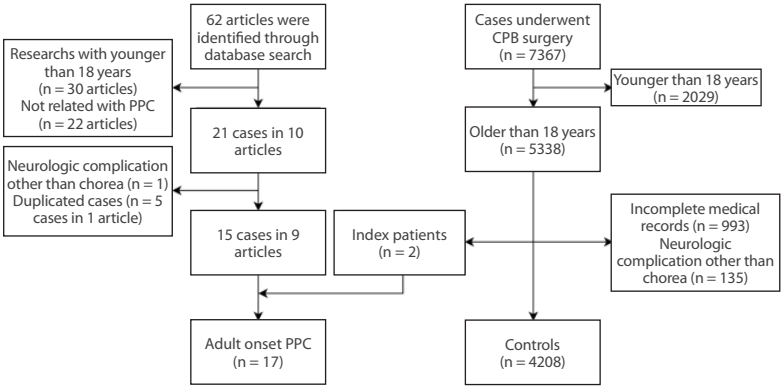
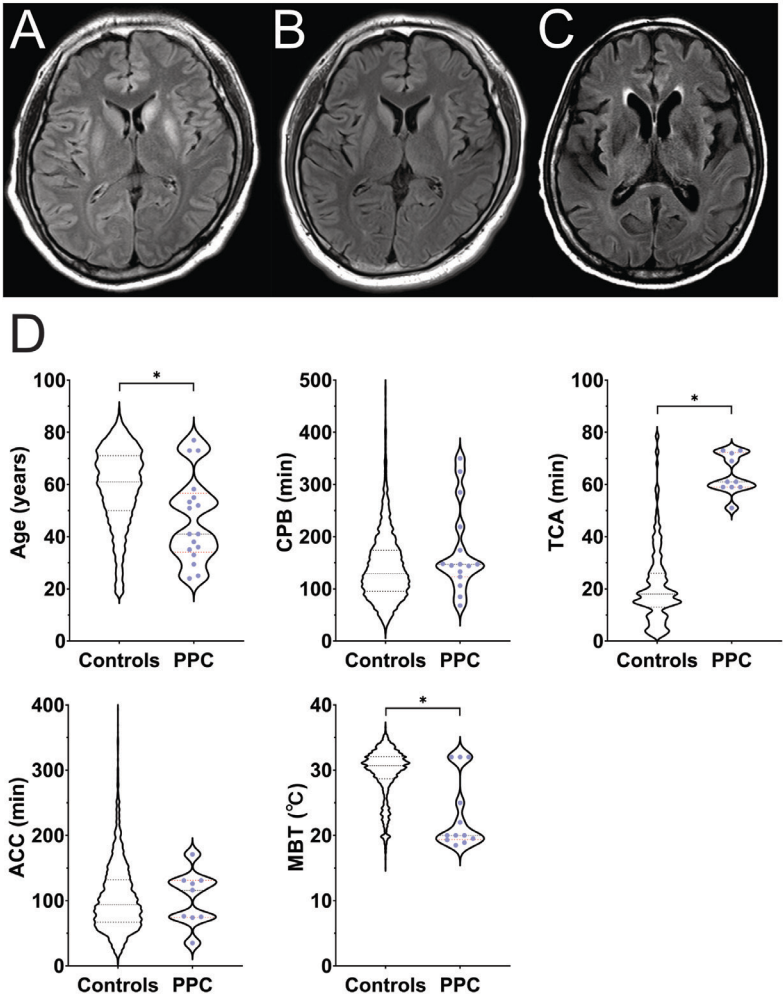
Background: Post-pump chorea (PPC), defined as the development of chorea after major cardiac surgery utilizing cardiopulmonary bypass (CPB), has been rarely reported in adults.
Methods: We compared 17 patients with adult-onset PPC to controls who did not develop chorea after cardiac surgery with CPB. Two patients were enrolled using hospital based data and 15 were collected by a systematic literature review. The controls without chorea after CPB (n = 4,208) were collected using hospital based data.
We described the clinical and surgical features of adult-onset PPC and compared them with those of the controls.



Results: Ten of 17 PPC patients were male, the mean age was 46.8 years, and the mean onset latency was 6.0 days. The adult-onset PPC patients were younger (46.8 ± 16.7 vs. 59.1 ± 15.0, $p = 0.001$), had a lower minimum body temperature (23.3 ± 5.5 vs. 29.7 ± 3.7, $p < 0.001$) and a longer total circulatory arrest time (63.7 ± 7.5 vs. 21.0 ± 14.6, $p < 0.001$) than controls.
Forty-three percentage of patients with adult-onset PPC had persistent chorea on follow-up, and these patients showed a higher rate of abnormal initial brain MRI compared with the patients with good clinical outcomes ($p = 0.041$).



Conclusions: The onset age, onset latency, underlying disease, treatment response, and surgical features were variable among PPC patients, while abnormal initial brain MRI was associated with persistent chorea. Pooling more cases through multicenter efforts will hopefully provide more knowledge on the underlying pathophysiology, prevention, and management of PPC.

P85
Blocking tics in Gilles de la Tourette syndrome

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Background: Patients with Gilles de la Tourette syndrome (GTS) may experience blocking tics (BTs) defined as recurrent, brief cessations of motor acts. The aim of this study was to assess the prevalence, age of onset, and clinical correlates of BTs in GTS patients.
Methods: We performed a one-time registration study in a cohort of 195 consecutive GTS patients aged 5–66 years (mean age: 15.0±9.2; 47 females, 24.1%). All patients were personally interviewed and examined.
Results: At least one BT occurred at some point in the lifetime of 73 patients (37.4%) with a mean age of onset of 10.4±5.9 years. BTs occurred an average of 4.8±5.3 years after tic onset. The most common BT was cessation of walking (n=59, 80.8%), followed by speech (n=19, 26.0%), running (n=18, 24.7%), and writing (n=9, 12.3%). Most of the patients (n=52, 71.2%) reported cessation of only one activity. Clinical associations of BTs included more severe tics, overall greater number of tics, and, to a lesser extent, higher age at evaluation and comorbid obsessive-compulsive disorder.
Conclusions: BTs represent complex tics, early and common symptoms of GTS, and are associated with a more severe form of GTS.

Ataxias, hereditary spastic paraparesis

P86
Analysis of diffusion tensor parameters in spinocerebellar ataxia type 3 and type 10 patients

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Background: There is a dearth of studies of spinocerebellar ataxias (SCAs) and diffusion tensor magnetic resonance imaging (DTI).
The aim of the study was to analyze changes observed in DTI parameters and correlate these to clinical findings in SCA3 and SCA10 patients.
Methods: SCA3 (n = 19) and SCA10 (n = 18) patients were compared with a similar number of controls and assessed clinically and with the scale for the assessment and rating of ataxia (SARA) before undergoing the same MRI protocol.
TRACULA (TRActs Constrained by UnderLying Anatomy) software was used to analyze the DTI metrics FA, AD, RD and MD.
Results: More white matter fiber tracts with changes in diffusivity were found in SCA3 patients than in SCA10 patients. There was a reduction in AD in altered fiber tracts in SCA3 and a greater increase in RD in SCA10. In the SCA3 patients, FA was reduced in the corticospinal tract (CST) and inferior longitudinal fasciculus (ILF), but this was not observed in the SCA10 patients (Figure 1).
SARA score was correlated with DTI findings in SCA3 but not in SCA10.
Conclusions: Changes were observed in DTI for both SCA3 and SCA10 but were more widespread in SCA3. Our finding of myelin-sheath changes in SCA10 and secondary axonal changes in SCA3 may reflect the more rapid, aggressive clinical course of SCA3.

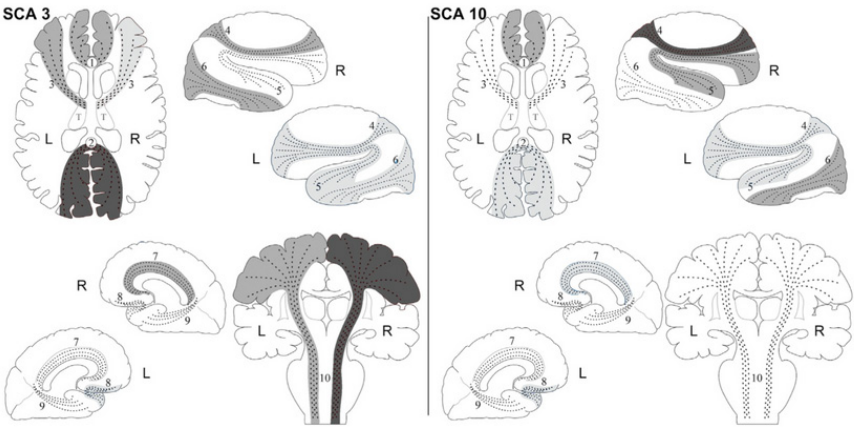

Figure 1. Brain white matter tracts in SCA3 and SCA10 patients: changes compared with controls
Source: The authors (2020)
Notes: The colours indicate the type of axonal lesion (reduced AD - dark gray) or demyelinating lesion (increased RD - light gray) or nonspecific change (reduced FA and/or increased MD - gray). Unaltered tracts are not colored.
Legends: 1 - forceps minor (FMi); 2 - forceps major (FMa); 3 - anterior thalamic radiation (ATR); 4 - parietal region of the superior longitudinal fasciculus (SLFp); 5 - temporal region of the superior longitudinal fasciculus (SLFt); 6 - inferior longitudinal fasciculus (ILF); 7 - cingulate fasciculus (CF): 8 - uncinate fasciculus (UNF); 9 - cingulum angular bundle (CAB); 10 - corticospinal tract (CST); R - right; L - left; SCA3 - spinocerebellar ataxia type 3; SCA10 - spinocerebellar ataxia type 10.

P87
New allelic heterogeneity in the spectrum of ataxia with oculomotor apraxia type 2

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Background: Ataxia with oculomotor apraxia type 2 (AOA2) is an inherited disorder caused by mutations within both alleles of the senataxin gene. Various mutations either in homozygous or compound heterozygous condition were so far identified in the associated gene SETX. SETX encodes a large protein called senataxin with a DNA-RNA helicase domain and a putative N-terminus protein interaction domain. Unlike other autosomal recessive cerebellar ataxia syndromes, levels of alpha-fetoprotein are nearly always elevated.

Methods: We report a case of 21 year old patient who presented with cerebellar ataxia, neuropathy and speech dysarthria. Patient had no family of ataxia. Patients underwent clinical examination, routine laboratory tests and brain MRI.
Ataxia comprehensive evaluation by Athena diagnostics was performed alpha fetoprotein level in serum was sent.
Results: Athena diagnostic genetic report showed heterozygous frame shift mutations in SETX gene, c.6729_6730;2 bp deletion of CA; Codon 2243-2244 and heterozygous missense mutation in SETX gene, C6683 C>T; p.Ser 2228 Leu (variant of uncertain clinical significance (VUS)). To determine if this variant was pathological further genetic test was performed on asymptomatic 3 family members.
Testing of 3 family members indicates that the likely pathogenic variant SETX c. 6729_6730 bp Deletion of CA and the previously reported variant of uncertain clinical significance(VUS) c. C6683 C>T, were inherited on opposite alleles and only the reportedly affected proband carried both variants.
This additional analysis showed association with disease for VUS. C.6683 C>T.
Alpha fetoprotein level was high at 56.6. Also conforming the diagnosis of Ataxia with oculomotor apraxia type 2 (AOA2).
Conclusions: This report extends the allelic heterogeneity of SETX mutations causing AOA2. This case report confirm that C.6683 C>T mutation is pathological. It has not been reported previously in the literature.

P88
Deregulated protein kinases in brain/PBMCs: Novel therapeutic targets in Friedreich's ataxia

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Background: Low levels of ubiquitously expressed iron binding frataxin protein in Friedreich's ataxia (FRDA) cause neurodegeneration and high oxidative stress which alter expression of numerous genes in patients.
In the present study, we aimed to identify protein kinases (PKs) in FRDA which can be targeted to elaborate disease pathogenesis and for therapeutics development.
Methods: Differentially expressed PKs (FDR<0.05; log2 ratio ≥ 1) were selected from Napierala et al. Dis Model Mech. 20171 in which gene expression profiling was done on 18 FRDA patients and 17 matched controls. The list of PKs, conserved in mouse and human, were extracted from

the UniProt database (Release: 2020_06; https://www.uniprot.org/docs/pkinfam.txt). To find tissue-wise gene expression, Protein Atlas Database was used. All comparisons and computational data analysis were performed using Python 3.8 and R statistical environment.
Results: Out of 614 differentially expressed genes, twenty PKs were identified in FRDA patients (FDR<0.05). The expression levels were varied from 1.0 (Homeodomain-interacting protein kinase 2; HIPK2) to 2.25 (polo-like kinase 1; PLK-1) folds. Protein atlas showed their distribution in the cerebral cortex, basal ganglia, midbrain, cerebellum and pons & medulla which are atrophied in FRDA (Table-1).
High expression of doublecortin-like kinase-1 (DCLK1) in the brain regulates microtubule polymerization2. FRDA patients showed lesser expression of DCLK1 than normal brain. Calcium/calmodulin-dependent protein kinase ID (CAMK1D) is involved in neuronal development and plasticity3 and is present in lower levels than normal levels. Similarly, enzymes HIPK2, CIT, MARK1 are expressed in FRDA patients (Figure-1).
Conclusions: Expression levels of selected PKs were altered in FRDA samples as compared with Protein Atlas. Oxidative stress in FRDA has been correlated to altered expression of genes including PKs which in turn can have strong implication in disease pathogenesis. Validation of these PKs in brain tissues of FRDA models will unveil new therapeutic targets to control the phenotype.

P89
Heterozygous Mutation in SPG7 gene: A case report

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Background: An autosomal recessive mutation in the SPG7 gene is associated with Hereditary Spastic Paraplegia (HSP). The heterozygous carrier with one functional copy typically does not show signs and symptoms. The patient in this case presented with typical features of spastic ataxia but his genetic testing revealed a single SPG7 gene mutation.
Methods: A 58-year-old male presented with blurry vision and progressive worsening of gait for the past 17 years. Physical exam showed gait abnormality with bilateral ataxia, mild spasticity, dysarthria, and tremors. Similar symptoms were also reported in his brother. Imaging was done, which showed marked cerebellar atrophy. A genetic test was negative for SCA 1,2,3,6 and 7 gene mutation. Whole-exome sequencing revealed a single gene mutation in the SPG7.
Results: The case illustrates the complexity of genotype/phenotype in SPG7 mutation. The pathophysiology is a disruption in the function of mitochondrial metalloproteases such as paraplegin, which results in axonal degeneration of the corticospinal tract (Zhang et al., 2018).

Making the right diagnosis is challenging for clinicians because of the overlap of genotype, symptoms, cellular pathways, and disease mechanism with other conditions that cause cerebellar ataxias.

The case reported ataxia without paraplegia, intermittent diplopia, and mild spasticity. The patient was worked up for SCA genes but further genetic testing revealed a single SPG7 mutation.

In a study by Pfeffer et al., 2014, compound and single heterozygotic mutations were seen in patients with transient diplopia and cerebellar ataxia. Sanchez-Ferrero et al., 2013, also reported the p. A510V variant of SPG7 that has a pathogenic role in single carriers.

Recently, SPG7 mutation is considered a common cause of autosomal recessive cerebellar ataxia with pronounced cerebellar features rather than spasticity (Synofzik et al., 2017).

Conclusions: Many studies report the complex spectrum of symptoms in SPG7 mutation but genotype/phenotype correlations are still unclear at present.

Tremors, Myoclonus

P90
Speech-induced action myoclonus: A single-center case series

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Background: Action myoclonus can occur in a wide range of neurological conditions; however, speech-induced action myoclonus is relatively rare, and has been described in only a few case reports. We sought to characterize this condition better by describing a case series at a single institution.
Methods: A retrospective review of electronic medical records from January 1989 to May 2020, at Mayo Clinic Rochester, identified nine patients with speech-induced action myoclonus. All were evaluated by experienced movement disorders neurologists and speech pathologists. Results of EEG, MRI, and movement disorders laboratory testing were reviewed and tabulated.
Results: The nine patients (four male) were median age 48 years (range 16-60), with median age of onset of 43 years (range 9-60). The diagnosis of speech-induced action myoclonus was often delayed, on average by five years. It was frequently mistaken for various conditions prior to diagnosis, including hemifacial spasm, stuttering, or functional speech disorder.
An associated neurological condition (progressive myoclonic epilepsy, idiopathic generalized epilepsy) or provoking factor (drug toxicity, chemical poisoning) was found in six patients, and in the remaining three patients it appeared to be idiopathic. The type of speech task that most strongly elicited myoclonus varied among patients, from spontaneous speech to reading aloud.
Five out of the nine patients had movement laboratory neurophysiology studies, and the presence of myoclonus was confirmed in all five. Musculature involved included facial (perioral/lower face), jaw (masseter), neck (platysma, sternocleidomastoid), larynx, and diaphragm. Of the five patients who were trialed on anti-myoclonic pharmacotherapy and had follow-up, four reported improvement.
Conclusions: Speech-induced action myoclonus is frequently mistaken for other speech or facial movement disorders. It may occur in isolation or with other neurologic conditions. Diagnostic clues include modulation with different speech tasks and rates. It can be confirmed by surface electrophysiology and anti-myoclonic pharmacotherapy should be considered.

Gait and Other Movement Disorders

P91
Pooled efficacy analysis of incobotulinumtoxinA for multipattern treatment of upper- and lower-limb spasticity in children and adolescents with cerebral palsy

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Background: This pooled analysis assessed the efficacy of incobotulinumtoxinA for lower-limb (LL) and upper-limb (UL) spasticity in children and adolescents with cerebral palsy (CP) using data from the first controlled injection cycle of two large, phase 3 studies, TIM (NCT01893411) and XARA (NCT02002884).

Methods: Ambulant and non-ambulant patients (2–17 years of age; uni- or bilateral CP; Ashworth Scale [AS] score ≥2 in clinical patterns for treatment) were randomised (2:1:1) to three incobotulinumtoxinA dose groups: 8, 6, 2 U/kg body weight (BW), maximum 200, 150, 50 U, per LL clinical pattern in TIM and per UL in XARA.

Additional multipattern treatment was allowed with total body doses up to 16–20 U/kg BW (≤400–500 U), depending on study and Gross Motor Function Classification System (GMFCS) level I–V. Changes from baseline in AS score and Global Impression of Change Scale (GICS) scores at Week 4 were assessed.

Results: In total, 603 patients with LL treatment from both studies (58.9% male, mean [SD] age 6.8 [4.2] years, BW 23.6 [13.5] kg, 27.2% GMFCS IV–V) and 350 patients with UL treatment from XARA (62.9% male, mean [SD] age 7.3 [4.4] years, BW 25.0 [15.0] kg, 30.9% GMFCS IV–V) were included. Improvements in AS score for the main LL/UL clinical patterns were seen with all incobotulinumtoxinA doses at Week 4 (all $p<0.0001$ vs baseline except adducted thigh at

8 U/kg). Significant improvement in AS score for the main UL clinical pattern was noted in the 8 U/kg versus the 2 U/kg dose group (p=0.004). Investigator's, child/adolescent's and parent/caregiver's GICS scores confirmed improvement in LL/UL spasticity at Week 4.
Conclusions: IncobotulinumtoxinA provides effective multipattern treatment of LL/UL spasticity in paediatric patients with CP (GMFCS I–V).
Funding: Funded by Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany.

P92
Efficacy and safety of incobotulinumtoxinA in the treatment of lower-limb spasticity in Japanese patients

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Background: This study aimed to confirm the efficacy and safety of incobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals GmbH) treatment for post-stroke spasticity in the lower limb (LL) in Japanese patients, using the modified Ashworth Scale spasticity score for the plantar flexors (MAS-PF).
Methods: This phase 3, double-blind, placebo-controlled, randomised, multicentre study (CTI-153030) included an open-label lead-in tolerability period (LITP) of one injection cycle (IC) of 400 U incobotulinumtoxinA in 11 patients and a main period (MP) that randomised 208 patients to receive one injection of incobotulinumtoxinA (n=104) or placebo (n=104). Dosing was 400 U, as determined by a safety assessment at the end of the LITP.
After the MP, 202 of these patients were enrolled in an open-label extension (OLEX) of three ICs, each 10–14 weeks in duration (cycle 3 was fixed at 12 weeks).
Changes in MAS-PF were assessed from baseline to Weeks 1, 4, 6, 8 and 12 for the MP and at the end of each cycle in the OLEX.
Results: Tolerability of incobotulinumtoxinA was assessed as "good" or "very good" in all LITP patients. Efficacy of incobotulinumtoxinA (400 U) vs placebo was confirmed by area under the curve of the changes in MAS-PF throughout the MP.
IncobotulinumtoxinA patients' MAS-PF was significantly greater vs placebo (LS mean: –8.40 and –5.81; respectively [p=0.0041]). The mean (standard deviation) changes in MAS-PF from study baseline to end of OLEX cycle 1, 2 and end of study were –0.51 (0.63), –0.60 (0.65) and –0.83 (0.77), respectively, showing improvement across repeated ICs. No safety concerns were observed.

Conclusions: This study confirmed the efficacy of incobotulinumtoxinA in a Japanese population with LL spasticity and showed that incobotulinumtoxinA at 400 U had a favourable safety and tolerability profile.
Funding: Funded by Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany.

P93
Safety of incobotulinumtoxinA for treatment of upper- and lower-limb spasticity in children/adolescents with cerebral palsy: Pooled phase 3 analysis

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Background: This analysis assessed the safety and tolerability of repeated incobotulinumtoxinA treatment for lower-limb (LL), upper-limb (UL), or combined LL/UL spasticity in ambulant and non-ambulant children/adolescents with cerebral palsy (CP) using pooled data from three large, phase 3 studies.
Methods: Patients with spasticity (age 2–17 years; uni- or bilateral CP; Gross Motor Function Classification System [GMFCS] level I–V; Ashworth Scale score ≥2 in clinical patterns for treatment; clinical need for treatment) were enrolled. Patients received total body incobotulinumtoxinA doses of 16 U/kg body weight (BW, ≤400 U) for LL spasticity in 2 injection cycles (ICs) in TIM (NCT01893411). In TIMO (NCT01905683), TIM completers and new recruits received 4 ICs with 16–20 U/kg (≤400–500 U) for LL or combined LL/UL treatment. In XARA (NCT02002884), patients received 4 ICs with 16–20 U/kg (≤400–500 U) for UL or combined LL/UL treatment. Adverse events (AEs) were assessed.
Results: Overall, 907 patients (59.6% male, mean [SD] age 6.7 [4.2] years, BW 23.3 [13.9] kg) received multipattern treatment; 753 patients (83.0%) completed the studies and received ≤6 ICs. Across all ICs, 363 (40.0%) experienced an AE; 33 (3.6%) had ≥1 treatment-related AE. The most common AEs were nasopharyngitis (79 patients, 8.7%), bronchitis (42 patients, 4.6%)

and upper-respiratory-tract infection (35 patients, 3.9%). Serious AEs (SAEs) were reported for 49 patients (5.4%) while AEs of special interest (AESIs) reported in >1 patient included muscular weakness (6 patients, 0.7%), dyspnoea, constipation and dysphagia (3 patients, 0.3% each). Incidence of AEs, SAEs or AESIs did not increase with repeated dose. No deaths were reported.

Conclusions: IncobotulinumtoxinA was safe and well-tolerated for LL, UL, or combined multipattern treatment over up to 6 ICs in a comprehensive population of paediatric patients with spasticity (GMFCS level I–V).

Funding: Funded by Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany.

P94
Absence of neutralising antibody formation during incobotulinumtoxinA treatment of spasticity in botulinum toxin-naïve children with cerebral palsy: Phase 3 analysis

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Background: Neutralising antibodies (NAbs) have been linked to secondary non-response to botulinum neurotoxin type A (BoNT-A) injections; this controversial issue is of special concern when treating conditions like paediatric spasticity. We investigated NAb formation in three large, phase 3 studies with incobotulinumtoxinA, a BoNT-A with no complexing proteins, in children/adolescents with cerebral palsy (CP) who received multipattern spasticity treatment.

Methods: Patients with lower-limb (LL), upper-limb (UL), or combined LL/UL spasticity (2–17 years of age; uni- or bilateral CP; Ashworth Scale score ≥2 in clinical patterns for treatment) were enrolled. Patients received total body incobotulinumtoxinA doses of ≤16–20 U/kg body weight (BW, ≤400–500 U) depending on the study (TIM: NCT01893411; TIMO: NCT01905683; XARA: NCT02002884) and Gross Motor Function Classification System level I–V, for up to six in-

jection cycles (ICs). The occurrence of NAbs against BoNT-A was investigated in those patients ≥21 kg BW at screening and end of study. Blood samples were analysed using a fluorescence immunoassay (FIA) for antibodies, and positive samples were then tested for NAbs using a hemidiaphragm assay.

Results: Overall, 907 patients (59.6% male, mean [SD] age 6.7 [4.2] years and BW 23.3 [13.9] kg) received treatment**.** In total, 386/403 patients (95.8%) and 318/422 patients (75.4%) with BW ≥21 kg were tested using FIA at screening and end of study, respectively, with 150/403 (37.2%) being toxin-naïve at screening.

Eleven individual patients tested positive for NAbs at screening and/or end of study, all of whom had previously been treated with other BoNT-As (onabotulinumtoxinA/abobotulinumtoxinA).

None developed a secondary non-response to incobotulinumtoxinA. No toxin-naïve patients developed NAbs after incobotulinumtoxinA treatment.

Conclusions: NAb formation was not observed in toxin-naïve children/adolescents with CP treated with up to six ICs of incobotulinumtoxinA.

Funding: Funded by Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany.

P95
Very long standing seronegative stiff person syndrome (SPS): A report of clinical and electrophysiological features

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Background: Stiff person syndrome (SPS) is a rather rare autoimmune disorders of central nervous system. This disorder often causes a lot of disability to the patients. Seropositive stiff person syndrome can be easily diagnosed when SPS specific antibody is found in appropriate clinical setting. In absence of SPS specific antibody, the electrophysiologic study is valuable and should be done to confirm diagnosis of seronegative SPS.

Methods: Case report. Needle electromyographic features before and after received diazepam. Laboratory work up and cerebrospinal fluid exam.

Results: 58 year-old man presented with low back pain with concomitant stiffness and marked pain of abdominal wall and both thighs. When he walked, he would have spasms of abdominal wall, buttocks and thighs and had to lie down for rest. His symptoms progressed in several months then became constant. He underwent surgery for spondylolisthesis twice without improvement. Eight years later, he was sent for Neurology consultation. Physical examination

showed lumbar lordosis, palpating stiffness and hypertonia of entire pasaspinal muscles, abdominal wall, bilateral gluteal and thigh muscles with atrophy of bilateral thighs. Brain and MRI findings were unremarkable. Laboratory and cerebrospinal fluid exam result including autoimmune neurological antibody panel were unremarkable. Needle electromyographic result showed spontaneous continuous motor unit activity at left vastus lateralis and semitendinosus muscles at the same time. The continuous motor unit activity diminished dramatically after he received 10 milligrams diazepam intravenously for 90 seconds and then was absent at 105 seconds. He did not receive IVIg due to financial problem and refused any immunosuppressive agents. He is currently treated with diazepam and baclofen orally.
Conclusions: When encountering a patient who presented with muscle stiffness, one condition that should be in the differential diagnostic list is SPS. Electrophysiologic study is valuable in confirming the diagnosis especially in seronegative case.

P96
Effect of varenicline and smoking reduction on tardive dyskinesia

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Background: Varenicline, a partial agonist at specific nicotine receptors that is effective in smoking cessation, reduces drug-induced dyskinesias in animal models suggesting promise as a treatment for tardive dyskinesia (TD). But this action may be obscured by fluctuations in plasma levels of some antipsychotics induced by hydrocarbons in cigarette smoke. The effect of varenicline-assisted smoking reduction on TD was examined in a pilot study.
Methods: Three schizophrenia patients with TD who were smokers and received long-acting injectable paliperidone underwent an open trial of varenicline. After a 2-week baseline, subjects received varenicline 1 mg twice daily. Changes (mean ± SD) in AIMS, SAS and BAS scores, average daily cigarette consumption (TLFB) and carbon monoxide (CO) exhalation were measured after a 4-week varenicline stabilization period.
Results: Varenicline had no significant effect on mean AIMS (+1.0 ± 2.2), SAS (-0.7 ± 1.7) or BAS (+0.3 ± 0.5) scores after 4 weeks. Although smoking decreased on varenicline as expected (TLFB -6.3 ± 4.5; CO -6.0 ± 9.4ppm), no effects on ratings of TD or other drug-induced movement disorders were observed.
Conclusions: In contrast to animal models, no change in TD occurred in response to varenicline in 3 schizophrenia patients. Further investigations of cholinergic mechanisms in TD are worthwhile as other specific cholinergic receptor agents become available. Given potential

pharmacokinetic effects of smoking on antipsychotics other than paliperidone, treatment trials of TD should control for smoking status, while patients on antipsychotics receiving nicotine replacement therapies for smoking cessation should be studied further for changes in drug-induced movements.

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Which is the effects of virtual reality in vestibular dysfunction: A systematic review with meta analise

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Background: Individuals with chronic vestibular dysfunction may be unable to perform various activities of daily living causing a decrease in quality of life and deterioration of vestibular function (MICARELLI et al., 2019). Vestibular rehabilitation (VR) has been one of the most indicated interventions in reducing vestibular symptoms and improving body balance in individuals with vestibular dysfunction (PAVLOU et al., 2012).
This systematic review was conducted to the following central question: "What are the effects of vestibular rehabilitation with virtual reality on adults with vestibulopathy of any etiology?".
Methods: Combinations of words and appropriate truncations were selected and adapted for the databases: CINAHL, Cochrane Library, Pubmed/Medline, SCOPUS and Web of Science. Gray literature was also consulted through Google Scholar, Open Gray and Proquest.
To consider the eligibility of the studies to be included, the acronym PICOS was used: P) Adults aged 18 years or older with vestibulopathy of any etiology; I) Virtual reality; C) Control or comparison group (conventional rehabilitation); O) Improvement or worsening of vestibular dysfunction, assessed through validated questionnaires; S) Randomized controlled studies, non-randomized, quasi-randomized controlled studies, and observational cohort and case-control studies.
The bias of the included studies was assessed using the Cochrane Risk of Bias Tool, and the certainty of the evidence was assessed by the GRADE tool.
Results: Among 3939 studies identified, 10 articles were selected for qualitative synthesis and six studies were included in the meta-analysis. When comparing the initial period with the post-intervention period, there was a positive association in all questionnaires used, except in the SOT questionnaire, which despite demonstrating a global effect of improving balance but did not demonstrate statistical significance.

Conclusions: Virtual reality evidenced to be a good alternative for therapy for the treatment of vestibular disorders of different causes, with an improvement of the condition when patients were undergoing this therapy.

P98
Gait hesitation and instability scale with difficulty of an augmented-reality task in Parkinson Disease

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Background: Gait instability is a significant contributor to morbidity in Parkinson Disease (PD), and is worsened by movement initiation, turns, narrow passages, obstacles, and dual-tasking. It is affected by medication state, disease progression, and PD phenotype. In order to optimally elicit instability, there is a need for standardized gait tasks of adjustable difficulty. We used a wireless augmented-reality headset to administer a gait task of three difficulties, and demonstrate feasibility of simultaneous wireless recording of EEG, LFP, and kinematics. We investigate whether gait parameters like cadence or step time coefficient of variation (CoV) correlate to task difficulty, and, whether there are neural correlates of gait instability.
Methods: One participant with PD and externalized right STN DBS directional leads was recruited. LFPs were recorded from 8 contacts on 4 rings (1, 3, 3, and 1 per ring). Also, 13 EEG channels, head position and acceleration, and waist acceleration were recorded. The digital gait task consisted of laps around a 2m by 9m course, "easy" without obstacles, "medium" with a digital doorway and several obstacles, and "hard" with an additional cognitive dual-task. From video, activity was manually labeled as sitting, standing, walking, or hesitation.
Results: Percent time hesitating increased with course difficulty (0 to 31.9 to 62.4%), cadence decreased (113.5 to 90.7 to 87.6 steps/min), and straight-segment step time CoV increased (8.1 to 22.6 to 29.7%). Qualitatively, hesitation had a distinct LFP correlate in 2/3 directions of the DBS lead, but was indistinguishable from walking in the third direction.
Conclusions: Preliminary work demonstrates that a wireless augmented reality gait task of varying difficulties can trigger hesitation and modulate gait parameters appropriately, with neural correlate. This approach allows task difficulty to scale with disease progression, medication state, or other factors. We anticipate this approach will be valuable for future investigations of PD gait.

Rehabilitation, Nursing/Physiotherapy, Other Allied Health; Patient Participation

P99
Feasibility and safety of a tele-yoga intervention for individuals with Parkinson's disease: A pilot study

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Background: Despite current available treatments, individuals with Parkinson's disease (PD) experience motor and non-motor symptoms along with access-related barriers to care. Easily accessible adjunct treatments that can address both types of symptoms while simultaneously facilitating access are warranted. Thus, the objective of this study was to investigate the feasibility of a one-on-one tele-yoga intervention program for individuals with PD.
Methods: Individuals with PD were enrolled in a single group pilot feasibility study that was conducted remotely via videoconference. It consisted of the following components: 1) a baseline assessment session, 2) a 6-week waiting period, 3) a second assessment session, 4) a 6-week tele-yoga intervention period, 5) a post-intervention assessment session, 6) a 6-week follow-up period, and 7) a final assessment session. The tele-yoga intervention was delivered live, one-on-one, for thirty minutes twice weekly and consisted of breathing exercises, postures, and relaxation exercises. Primary outcomes included adherence, adverse events, technological challenges, usability, and enjoyment. Secondary outcomes included measures of anxiety, depression, quality of life, sleep, symptom severity, and physical function but are not being presented.
Results: To date, nine individuals have completed the intervention and one participant dropped out. Adherence to the yoga sessions was approximately 95%. No significant adverse events occurred. Minimal technological challenges occurred with the most common being a delay in the audio/video feed. Mean usability was 74.17±19.08 on the systems usability scale indicating good usability. Mean enjoyment of the yoga intervention on a zero to ten scale with ten being the most enjoyment possible was 8.67±1.22.
Conclusions: While minimal technological challenges occurred, high intervention adherence and enjoyment paired with good usability indicated the tele-yoga intervention was feasible and acceptable. No significant adverse events occurred indicating that the tele-yoga intervention was safe. Therefore, the implementation of a one-on-one tele-yoga intervention for individuals with PD is safe and feasible.

P100
Using wearable smartwatch to track the exercise compliance and intensity of a community-based aerobic endurance training program

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Background: The aerobic endurance training (AET) exercise was reported to be more beneficial when compared with general exercise for people with Parkinson's disease (PD). The training intensity of AET was usually targeted at 40-60% heart rate reserve (HRR). It is therefore important to record the exercise compliance and the heart rate during exercise for successful training program.
The objectives of the present study are:
1) to compare the exercise record of the written exercise diary and the wearable smartwatch;
2) to examine the feasibility of tracking the training intensity with the wearable smartwatch.
Methods: A group of seventeen patients with PD (age 65.7 ± 8.5 years) was recruited for the study. The participants received AET under the supervision of physiotherapists for 6 weeks. The participants then carried out AET in the community environment for 150 minutes per week for 20 weeks. The wearable smartwatch (A370 from Polar Electro Oy, Finland) and an exercise diary were allocated to the participants to record their exercise compliance.
Results: There was no difference in recording the exercise duration per week by the smartwatch (mean duration: 116.0 ± 25.9 minutes) and exercise diary (mean: 109.6 ± 31.1 minutes). There was no difference between the smartwatch and exercise diary for the total number of records during the 20-week of AET.
However, the record taken by the smartwatch in each participant (94.5 ± 44.1 records) was nearly double the 53.2 ± 28.3 records of the exercise diary. The training intensity recorded by the smartwatch was 47.3 ± 3.4% of HRR.
Conclusions: Exercise compliance could be recorded by the smart watch and exercise diary. PD participants could have preferred to use the smartwatch to record their exercise compliance than the conventional written diary. The training intensity could be recorded by the smartwatch.