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Comparative Safety of Istradefylline Among Parkinson's Disease Adjunctive Therapies: A Systematic Review and Meta-Analysis of Randomized Controlled Studies

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Istradefylline has demonstrated a significant reduction in "OFF" time when used as an adjunct to levodopa/carbidopa in patients with Parkinson's disease (PD). A systematic review was updated with additional RCTs 1/1/2010-4/15/2019 to evaluate the safety of istradefylline vs. other PD adjuncts. Pair-wise meta-analysis and Bucher indirect comparisons were used to generate estimates of relative safety. Results are presented as OR [95% CI] relative to istradefylline. Overall, 57 RCTs involving 11,517 patients were included for meta-analysis. Istradefylline data were extracted from clinical study reports. At 40mg, istradefylline demonstrated significantly lower odds of dyskinesia and somnolence compared to dopamine agonists (DAs) (1.30 [1.01, 1.69] and 2.50 [1.28, 5.00]) and lower odds of hypotension compared to monoamine oxidase type B inhibitors (8.33 [1.67, 50.00]). At 20mg, the odds of dyskinesia were significantly lower for istradefylline vs. catechol-O-methyl transferase (COMT) inhibitors (1.52 [1.09, 2.13]), DAs (1.61 [1.16, 2.22]), and all interventions (1.45 [1.06, 2.00]). Relative to istradefylline, amantadine had significantly increased odds of hallucinations (40mg: 3.57 [1.30, 10.00]; 20mg: 4.76 [1.64, 14.29]), and insomnia and withdrawals due to treatment emergent adverse events (TEAEs) at 20mg (8.33 [1.06, 50.00] and 2.86 [1.18, 6.67]). The odds of overall incidence of TEAEs including constipation, dyskinesia, hallucination, hypotension, insomnia, orthostatic hypotension, and somnolence were significantly lower for istradefylline compared with COMT inhibitors (40mg: 1.33 [1.03, 1.75]; 20mg: 1.32 [1.01, 1.72]) and amantadine (40mg: 3.45 [1.85, 6.25]; 20mg: 3.33 [1.82, 6.25]). Istradefylline is associated with a generally favorable safety profile relative to other adjunct medications in this study.

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Real-world benefits of APO-go® POD in advanced Parkinson’s disease (PD) – a patient case study

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Background Continuous subcutaneous apomorphine (APO) infusion is an effective and well-tolerated therapy for advanced PD. APO-go® infusion (Britannia Pharmaceuticals) is administered using a portable mini-pump with the solution contained in pre-filled syringes (PFS). A new method of administration, APO-go® POD, is now available with the solution supplied in a cartridge. The first UK patient was initiated in 2023.

Methods The practical benefits of APO-go® PFS and POD administration are compared, and illustrated with a case study from our centre of a patient who transitioned from PFS to POD.

Results The time required to set up the infusion with APO-go® POD is 34 seconds (8 steps), compared to 1 minute 48 seconds for PFS (12 steps), a reduction of 1 minute 14 seconds. The POD system requires fewer ancillaries and does not require liquid transfer as it attaches directly to the pump. At our centre, a 52-year-old female patient who had had PD for 10 years commenced APO-go® PFS infusion in January 2023. This effectively controlled her symptoms, but with impaired dexterity she struggled with the set-up (liquid spillage) and disposal of ancillaries, particularly when travelling. She feels that the transition to POD has saved her time, is easier to set up in the morning, and there is less wastage.

Conclusions This case highlights the practical benefits the POD system can provide for PD patients in their daily lives. Set-up time and steps are reduced with the POD system, streamlining the administration process, making it easier for patients, and promoting independence.

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What change to expect in duration of benefit per dose when switching from IR CD-LD to IPX203 (ER CD-LD)

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Objective: To investigate if duration of benefit ("Good On" time) per dose during immediate-release (IR) carbidopa-levodopa (CD-LD) treatment predicts response to IPX203 conversion.

Background: IPX203, a novel oral extended-release (ER) CD-LD capsule, was developed to address levodopa's limited absorption window and short plasma half-life.

Methods: We performed post hoc analyses on Hauser diary data from 495 subjects who completed the RISE-PD phase 3 clinical trial. The patient population was rank-ordered and divided into quartiles based on "Good On" time per dose at the end of IR CD-LD dose optimization. Mean end of study (EOS) "Good On" time per dose values were then compared between IPX203 and IR CD-LD–treated groups for each quartile.

Results: Mean "Good On" times per dose for each quartile at the end of the IR CD-LD dose optimization phase were 1.35, 1.91, 2.36, and 2.96 hours. For IR CD-LD patients, EOS mean "Good On" times per dose were 1.71, 2.06, 2.34, and 2.93 hours. For IPX203 patients, EOS mean "Good On" times per dose were 3.16, 3.44, 4.02, and 4.55 hours. Mean differences in "Good On" time per dose between IPX203 and IR CD-LD were 1.53h, 1.38h, 1.85h, and 1.56h for each quartile, respectively.

Conclusions: Regardless of the duration of efficacy observed with IR CD-LD, measured as "Good On" time per dose, the improvement in duration of benefit observed with IPX203 remained similar, with an overall mean increase of 1.58 hours per dose. These results may help care providers plan conversion regimens and anticipate clinical responses.

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PARKINSON`S DISEASE, A LONG-TERM SEQUELA OF NEUROGENIC ORTHOSTATIC HYPOTENSION WITH CARDIAC SYMPATHETIC DENERVATION

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Introduction: Idiopathic neurogenic orthostatic hypotension is a rare disorder of the autonomic nervous system that significantly impacts the quality of life. The natural history of neurogenic orthostatic hypotension varies and may evolve into a central synucleinopathy. There is a need for robust and pathophysiologically relevant biomarkers of preclinical central synucleinopathies. In this report, we describe the long-term follow-up of patients with neurogenic orthostatic hypotension and imaging evidence of cardiac sympathetic denervation by 123I-metaiodobenzylguanidine single photon emission tomography (Cardiac 123I-MIBG SPECT)

Methods: Patients with orthostatic hypotension underwent clinical autonomic evaluation and were diagnosed with idiopathic neurogenic orthostatic hypotension. Cardiac 123I-MIBG SPECT was performed as part of the diagnostic algorithm to assess sympathetic innervation. Ten patients with neurogenic orthostatic hypotension had cardiac sympathetic denervation and were followed for the development of Parkinson's disease or neuroimaging evidence of central dopamine deficiency by 18F-DOPA positron emission tomography.

Results: During a mean follow-up of 5.6 years, all patients showed clinical or neuroimaging signs of central dopamine deficiency: Seven were diagnosed with Parkinson's disease; three showed non-diagnostic minimal extrapyramidal signs with unilaterally reduced 18F-DOPA-uptake. Among 5 patients tested for genetic mutations related to Parkinson`s disease, four were GBA mutation carriers.

Conclusions: In this series, the majority of patients with neurogenic orthostatic hypotension and imaging evidence of cardiac sympathetic denervation progressed to Parkinson's disease during follow-up, and the remainder developed clinical or neuroimaging evidence of nigrostriatal dopamine deficiency. This form of neurogenic orthostatic hypotension represent a body-first course toward Parkinson's disease via the sympathetic route.

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Long-term follow-up of patients with advanced Parkinson’s disease treated with levodopa–entacapone–carbidopa intestinal gel infusion (LECIG) in Sweden

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Background

Levodopa–entacapone–carbidopa intestinal gel infusion (LECIG) was approved by the Swedish Medical Products Agency in 2018 for the management of advanced Parkinson’s disease (PD). We previously reported initial experience with LECIG treatment at our centre in 24 patients treated for a median of 305 days.1 Here we report long-term data for this cohort who have been treated with LECIG for up to four years.

Methods

A retrospective, observational study of 24 patients (11 female, 13 male). Medical records were examined regarding gender, age, time since PD diagnosis, LECIG treatment duration, LECIG infusion dosage, adverse events and device complications.

Results

Patients had a mean duration of PD of 16 years and a mean age of 69.2 years at the start of LECIG treatment. Of the original 24 patients, 10 remain on LECIG treatment and one has paused due to problems with gastrointestinal access. Mean time on treatment is currently 26.5 months, with 10 patients continuing LECIG treatment. To date, three patients have received LECIG treatment for over four years. Of the 14 patients who stopped treatment, eight died. Three patients stopped during treatment initiation due to diarrhoea. Of the patients still receiving treatment, the most recent PDQ-8 score taken had a median of 12.

Conclusions

Our study is the first to present long-term data on the use of LECIG for up to four years in patients with advanced PD and indicates that it is generally well-tolerated in long-term treatment.

Reference

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Prescription patterns in treatment of Parkinson’s disease in tertiary centers in Poland

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There are several medications available for Parkinson’s disease treatment. The approach to the pharmacotherapy has been modified due to levodopa phobia two decades ago and dopamine agonist phobia recently. The aim of our observational, retrospective, multicenter study was to show how PD specialists in Poland treat PD patients nowadays and how the literature warnings influenced their practice. 494 patients took part in our study (Male: 301, Female: 193). Their mean age was 64.75 years (SD 10.62, 27-89), mean H-Y score was 2.45 (SD 0.68, 1-5) and mean duration of the disease was 9.54 years (SD 5.80, 1-30). 465 patients were treated with LD (mean dose 810.58mg), 292 with DA (ropinirole – 176 (mean dose 8.64mg), pramipexole – 105 (mean dose 1.76mg), piribedil - 8, rotigotine - 3), 202 with MAO-B inhibitors (rasagiline 198, selegiline 4), 197 with amantadine, 7 with entacapone and 4 with anticholinergics. 119 patients were on PD monotherapy, 152 were treated with two medications and 223 were treated with three or more drugs for PD. Patients were divided into subgroups depending on their HY score, age and duration of the disease, then pharmacotherapy of each group was analyzed showing that in every group levodopa was most often prescribed drug and remains a gold standard in treatment of PD in tertiary centers in Poland. Dopamine agonists were the second most frequently prescribed group of medications in our study, although they were less frequently used in older population (70 years old) and with HY score of 3 or more.

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Multiparametric cerebellar radiomic biomarkers for diagnosing Parkinson’s disease

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Objectives A growing body of research has provided clinical, pathological, and neurophysiological findings, unequivocally establishing a link between the cerebellum and Parkinson’s disease (PD). This study aimed to investigate the diagnostic potential of multiparametric magnetic resonance imaging (MRI) radiomics derived from the cerebellum.

Methods This retrospective study collected data (n=618) from two datasets. The Parkinson`s Progression Markers Initiative (PPMI) provided the training set, comprising healthy controls (HC, n=156) and PD patients (n=162). The results were subsequently validated using the test set data from an in-house dataset in Dalian, China, which included 146 controls and 154 PD patients. MRI radiomic features (n = 883) were extracted from the grey and white matter of the cerebellum. Three diagnostic models were developed: a cerebellar gray matter model, a cerebellar white matter model, and a combined cerebellar gray and white matter model.

Results The area under the receiver operating characteristic curve (AUC) analyses revealed that the combined model (AUCs 0.987; Sensitivity 0.951; Specificity 0.911) demonstrated superior predictive performance compared to the gray matter model (AUCs 0.897; Sensitivity 0.873; Specificity 0.921, p = 0.0392) and white matter model (AUCs 0.892; Sensitivity 0.863; Specificity 0.921, p = 0.0486) in the training set. Noteworthy radiomic features contributing to PD development included dependence variance and run variance domains in the white matter, as well as mean squared and gray level normalized domains in the gray matter.

Conclusions In conclusion, this study underscores multiparametric cerebellar MRI radiomics may have an incremental diagnostic value as a biomarker for PD.

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Role of rhythm perception and posture disturbances in daily life of patients with Parkinson`s disease

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Walking disability in Parkinson disease is secondary to hypometric stride, postural and rhythmic disturbances. However, there is significant heterogeneity between patients which is rarely taken into account in rehabilitation.

Methods
Several studies have been carried out on different patient populations 1. Assessment of difficulties in performing rhythmic movements in daily life using specific self-questionnaires 2. Evaluation of the abilities of perceive and reproduce rhythms with BASTAA battery (Battery for the Assessment of Auditory Sensorimotor and Timing Abilities) 3. Evaluation with the miniBEST scale of postural abilities in patients with freezing 4. Impact of a serious game on rhythmic activities (walking and speaking).

Results
Parkinson`s patients may have early difficulties to perform rhythmic motor movements that impact daily life. These disorders can be detected by a self-questionnaire or measured by a BAASTA battery. Freezing is responsible for falls only in the presence of abnormalities in postural control. The anomalies also concern to the perception of rhythm. Serious games developed to train the motor and sensory sides of rhythm improve speaking and walking skills.

Discussion
All of this work confirms the importance of rhythmic difficulties in the speech and walking disorders observed in Parkinson`s patients. It is therefore necessary to develop complete rehabilitation programs combining classic physiotherapy sessions with rehabilitation exercises and training of rhythmic skills using new technologies and the principles of therapeutic education. As postural disorders condition the risk of falling, it will be necessary for these patients to combine specific postural rehabilitation programs.

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Focused ultrasound rescues Parkinson patient following removal of implanted DBS hardware

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Background: Unilateral MRI-guided focused ultrasound (FUS) ablation has established efficacy in Parkinson's disease (PD). The pallidothalamic tract is gaining popularity as the target of choice.

Objective: To describe a single patient that underwent FUS pallidothalamic tractotomy for advanced PD following DBS hardware removal.

Methods: We present a patient with advanced PD and disabling symptoms that underwent FUS after removal of DBS due to severe infection. Unified PD Rating Scale (UPDRS) score in ON state was documented before and after the procedure.

Results: A 62 year old woman with a 12 year duration of PD underwent DBS 5 years previously at another center. She presented at our center with severe cellulitis and osteomyelitis at the electrode insertion site. After repeated antibiotic treatments with no improvement, DBS hardware was removed. Medication adjustments did not improve symptoms, while others, including apomorphine, caused psychosis. ON state UPDRS score was 37 with the patient suffering from severe rigidity and unable to stand due to impaired balance. As rescue treatment, unilateral FUS pallidothalamic tractotomy was performed. Following this procedure, ON state UPDRS score was decreased to 22. She was able to walk with no difficulty. No side effects were reported.

Conclusions: To the best of our knowledge this is the first case report demonstrating efficacy and safety of FUS pallidothalamic tractotomy in PD following removal of DBS hardware.Long term follow up is needed. FUS may offer hope for PD patients unwilling or unable to undergo DBS. Larger studies are needed to substantiate our findings.

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Type 2 Diabetes Mellitus comorbidity among Parkinson’s disease patients: A community based big-data study

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Background: Recent studies investigating the relationships between Parkinson’s Disease (PD) and Type 2 Diabetes Mellitus (T2DM) report inconclusive results, possibly due to small cohorts and disregard for the timing order of T2DM and PD diagnoses.

Objectives: To compare the risk of T2DM among a large-scale cohort of PD patients, to that of the general population, and to evaluate the effect of T2DM occurrence on PD patients` survival.

Methods: A population-based, large-scale cohort study, of incident PD patients members of Maccabi Health Services (MHS), a large Israeli HMO, who initiated anti-parkinsonian medications between 1.1.2000 and 12.31.2018. T2DM occurrence was collected from MHS T2DM-registry. Standardized-Incidence-Ratio (SIR), accounting for age, chronological-year, and sex, was calculated to compare T2DM risk in PD patients to that in the general MHS population. Cox regression was used to estimate the hazard ratio (HR) for death.

Results: The PD cohort comprised 11253 patients, 54.7% men, average age at PD diagnosis of 71(SD=11). Average follow-up was 6.8years (SD=4.5). During the study period, 3823 (33.97%) patients were diagnosed with new T2DM.prevalent T2DM in the PD cohort was significantly lower when compared to the reference population SIR=0.68 (95%CI; 0.66- 0.70). Out of 7976 patients, with no T2DM diagnosis at PD diagnosis. 666 (8.4%) developed T2DM during follow-up, and T2DM occurrence decreased their death risk HR= 0.70 (95%CI 0.62-0.78).

Conclusion: T2DM incidence and treatment apparently decrease PD incidence, risk, and death. Further studies are needed to investigate the cause for these findings, for potential implications for PD clinical management and prognosis.