Parkinson's Disease Research Review™

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Issue 30 - 2017

In this issue:

Abbreviations used in this issue:

CSF = cerebrospinal fluid; **DAT** = dopamine transporter; **MCI** = mild cognitive impairment; **PD** = Parkinson's disease; **REM** = rapid eye movement; **STN-DBS** = subthalamic nucleus deep-brain stimulation; **UPDRS** = Unified Parkinson's Disease Rating Scale.

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Welcome to the thirtieth issue of Parkinson's Disease Research Review.

The first two papers in this issue focus on cognitive impairment in PD, beginning with how to predict it in *de novo* disease, followed by the natural evolution of MCI (mild cognitive impairment) over 5 years. Two JAMA Neurol papers look at adjuncts to levodopa therapy (opicapone and safinamide) for managing patients with PD who have motor fluctuations. Researchers from the US and Italy have performed a thorough investigation of impulse control behaviours before and after STN-DBS for PD. This issue concludes with UK research testing an online, evidence-based algorithm to identify indicators of PD risk.

I hope you are finding these updates in PD research helpful in your everyday practice. Please don't hesitate to email your comments and suggestions to me.

Kind Regards,

Dr Paul Clouston

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Clinical variables and biomarkers in prediction of cognitive impairment in patients with newly diagnosed Parkinson's disease

Authors: Schrag A et al.

Summary: This analysis of the PPMI (Parkinson's Progression Markers Initiative) cohort study evaluated the use of clinical information and biomarkers as predictive factors for cognitive decline in patients with newly diagnosed PD. Cognitive performance (assessed using MOCA [Montreal Cognitive Assessment] score), demographic and clinical data, *APOE* status and biomarkers (CSF and DAT imaging results) were evaluated for their 2-year predictive value. The research included 390 patients with baseline and 2-year MOCA score data. Multivariate analyses showed that baseline age, UPSIT (University of Pennsylvania Smell Inventory Test) score, CSF amyloid ($A\beta_{42}$) to t-tau ratio and *APOE* status were associated with change in MOCA score over time. The five variables that showed the most significant associations with cognitive impairment (age, UPSIT, Rapid Eye Movement Sleep Behaviour Disorder Screening Questionnaire, CSF $A\beta_{42}$ level and caudate uptake on DAT imaging) allowed significant prediction of cognitive impairment at 2 years.

Comment: Dementia is the most devastating complication of PD leading to institutionalised care. MCI at PD presentation is a predictor for the development of dementia. This study used the large PPMI cohort to examine age, sense of smell measures, assessment of REM sleep behaviour disorder, depression scores, UPDRS part III, CSF amyloid to t-tau ratio and DAT imaging as risk factors for cognitive impairment at 2 years. They found that a combination of measures of all these variables allowed the most accurate prediction of the development of cognitive impairment (MCI or dementia) at 2 years. This may allow improved patient stratification for future clinical trials.

Reference: Lancet Neurol 2017;16(1):66–75

Abstract

Parkinson's Disease Research Review™

Independent commentary by Dr Paul Clouston, MB.BS. PhD FRACP

Paul is a general neurologist with interest in PD and neuromuscular disease. He is currently retired from practice for health reasons, but remains an affiliate at Brain-Mind Institute Parkinson's Research Clinic since 2013, and was a senior neurologist for Westmead Hospital, Western Sydney. He has extensive experience in general neurological practice and teaching neurological research, including clinical trials and publications, and has previous general management experience working as acting head of Westmead Department of Neurology, Director of EMG laboratory and an organiser of undergraduate medical student teaching.

Natural course of mild cognitive impairment in Parkinson disease

Authors: Pedersen KF et al.

Summary: This population-based research examined the incidence, progression and reversion of MCI in a cohort of patients with PD who underwent repeated neuropsychological tests over a 5-year period; 178, 175, 163 and 150 participants had evaluable data at baseline, 1 year, 2 years and 5 years, respectively. Criteria for PD-MCI were met by 20.2% of participants at baseline, and among the rest (n=142), the respective cumulative 1-, 3- and 5-year incidences of MCI were 9.9%, 23.2% and 28.9%. Among participants with baseline or incident MCI, 39.1% had progressed to dementia by the fifth study year. Compared with participants with normal cognition during the first year, a greater proportion of those with persistent MCI at 1 year converted to dementia (59.1% vs. 7.2%; adjusted odds ratio 16.6 [95% CI 5.1–54.7]). Conversion to normal cognition had occurred at study end in 27.8% and 24.2% of participants with baseline and incident MCI, respectively, but in only 9.4% of those with persistent MCI at two consecutive visits. Compared with participants with normal cognition, MCI reverters within the first 3 years of follow-up were more likely to develop subsequent dementia (adjusted odds ratio 10.7 [95% CI 1.5–78.5]).

Comment: This 5-year study confirms that the presence of MCI or its development is a strong predictor of subsequent PD dementia. What is of interest is that a significant minority of patients 'reverted' from MCI back to 'normal' on a subsequent examination, but even these patients were at increased risk of subsequent PD dementia.

Reference: Neurology 2017;88(8):767–74
Abstract

Dose-dependent progression of parkinsonism in manganese-exposed welders

Authors: Racette BA et al.

Summary: Movement disorders specialists undertook 1492 examinations in 886 welding-exposed workers in America, including 398 who had 606 follow-up examinations over ≤9.9 years. A positive association was seen between cumulative manganese exposure and progression of Parkinsonism, particularly progression of upper limb bradykinesia, upper and lower limb rigidity and impairment of speech and facial expression. Each milligram of manganese per m^3-year of exposure was associated with an annual change in UPDRS3 score of 0.24 (95% CI 0.10–0.38). The association appeared to be particularly apparent in welders who did flux core arc welding in a confined space and in those whose baseline examination was within 5 years of their first welding exposure.

Comment: The Parkinsonism associated with manganese exposure is atypical and does not respond to levodopa. There is controversy as to whether increased manganese exposure in welders can lead to Parkinsonism. This epidemiological study suggests that manganese exposure causes Parkinsonism in welders, and that this effect is cumulative.

Reference: Neurology 2017;88(4):344–51
Abstract

Fatigue in early Parkinson's disease

Authors: Ongre SO et al.

Summary: This prospective, population-based, longitudinal study of 181 patients with *de novo* PD and 162 matched controls examined fatigue during the first year after a diagnosis of PD. Compared with controls, the patients with PD reported more fatigue at both baseline and at 1 year. The patients with PD showed an improvement in mean Fatigue Severity Scale score from 4.4 to 4.0. Patients with PD who reported fatigue at baseline received higher doses of dopaminergic medication during follow-up, and those who received dopamine agonists experienced slightly better improvements than those who received levodopa. There was no evidence of a correlation between improvement in fatigue and change in disease severity, depressive symptoms, sleep problems, apathy or cognitive impairment.

Comment: Fatigue is a frequent nonmotor symptom of PD that is difficult to quantify. It must be distinguished from depression, daytime somnolence and apathy, all of which are also nonmotor symptoms of PD. In this study, fatigue was present very early in the illness and improved on medical treatment. Although somnolence is a recognised side effect of dopamine agonists, these drugs improved fatigue a little more than levodopa.

Reference: Eur J Neurol 2017;24(1):105–11
Abstract

Opicapone as adjunct to levodopa therapy in patients with Parkinson disease and motor fluctuations

Authors: Lees AJ et al., for the BIPARK-2 Study Investigators

Summary: Patients with PD who experienced signs of end-of-dose deterioration and had a mean total awake 'off' time of ≥1.5 hours (not including morning akinesia) were randomised to receive opicapone 25 mg/day (n=129), opicapone 50 mg/day (n=154) or placebo (n=144) in this 14- to 15-week phase 3 trial; 51 participants discontinued treatment during this double-blind phase. The respective least squares mean changes in 'off' time in the opicapone 25 mg/day, opicapone 50 mg/day and placebo arms were –101.7, –118.8 and –64.5 minutes, with a significant adjusted difference between the 50 mg/day and placebo arms (p=0.008), but not between the 25 mg/day and placebo arms (p=0.11). The 'off' time reduction was sustained throughout 1 year of open-label treatment with opicapone (n=286). The most common adverse events were dyskinesia, constipation and dry mouth.

Comment: Opicapone is a long-acting catechol *O*-methyltransferase inhibitor that can be given as a once daily dose. This is in contrast to entacapone, which must be taken regularly with levodopa either on its own or as the combination drug 'Stalevo'. The initiation of opicapone rather than entacapone may allow more flexibility in levodopa dosing, although it must be acknowledged that 'Stalevo' already has tablets of varied levodopa doses on the market.

Reference: JAMA Neurol 2017;74(2):197–206
Abstract

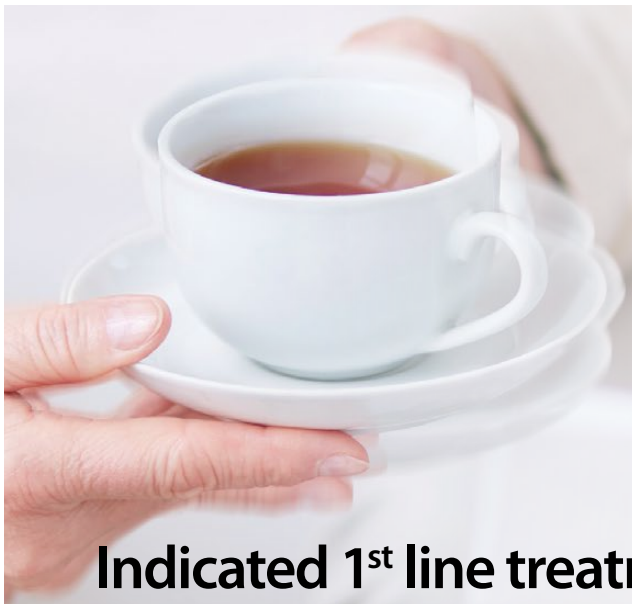
Assessment of safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson disease and motor fluctuations

Authors: Schapira AHV et al.

Summary: Patients with idiopathic PD on stable oral levodopa plus benserazide or carbidopa for ≥4 weeks with an 'off' time of ≥1.5 hours were randomised to receive adjunctive safinamide 50mg increased to 100mg if tolerated (n=274) or placebo (n=275) for 24 weeks; the study completion rates for the respective arms were 89.4% and 87.6%. Compared with placebo, safinamide was associated with a significantly greater mean increase from baseline in daily 'on' time without troublesome dyskinesia (primary endpoint; 1.42 vs. 0.57 hours [p<0.001]). Dyskinesia was the most frequently reported adverse event occurring in 14.6% of safinamide recipients and 5.5% of placebo recipients, and it was severe in 1.8% and 0.4%, respectively.

Comment: Unlike rasagiline and selegiline, which bind irreversibly, safinamide is a reversible monoamine oxidase B inhibitor as well as promoting glutamate release. This study confirms its efficacy in the management of patients with PD and motor fluctuations. So far this drug has been approved for use in Europe.

Reference: JAMA Neurol 2017;74(2):216–24
Abstract



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References: 1. Madopar Product Information, 29 February 2016 **2.** Hayes M et al. *Med J Aust.* 2010;192(3):144-149 **3.** Waldvogel D et al. *Swiss Archives of Neurology and Psychiatry.* 2014;165(5):147-5

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Long-term risk of falls in an incident Parkinson's disease cohort

Authors: Hiorth YH et al.

Summary: These authors reported on falls over a 7-year period for 181 drug-naïve participants with incident PD and 173 control participants from the Norwegian ParkWest study. Falls were reported by 64.1% of the patients during the study period, with a 7-year cumulative incidence of falls among 153 non-falling patients at baseline of 57.5% and the risk significantly increased compared with controls (relative risk 3.1 [95% CI 1.5–6.3]). Independent risk factors for incident falls during follow-up were higher age at baseline, a postural instability and gait difficulties phenotype at 1-year visit and follow-up time.

Comment: This is a case-control study looking at the risk of falls over 7 years in *de novo* PD. The risk of falling was three times that of the controls, with age and early gait problems, higher motor UPDRS scores and cognitive impairment conferring greater risk. No comment was made on gait freezing as a contributor to falls in these patients.

Reference: J Neurol 2017;264(2):364–72
Abstract

Impulse control behaviors and subthalamic deep brain stimulation in Parkinson disease

Authors: Merola A et al.

Summary: These researchers compared the pre- and postsurgical prevalences of impulse control behaviours (impulse control disorders, dopamine dysregulation syndrome and punding) in 150 consecutive patients with PD treated with STN-DBS, and identified associations with motor, cognitive, neuropsychological and neuropsychiatric endpoints. Impulse control behaviours prior to STN-DBS were associated with younger age (p=0.045) and male gender (p=0.001). Post-STN-DBS (average follow-up 4.3 years), there was a trend for impulse control behaviours to decrease from 17.3% to 12.7% (p=0.095), with significant improvements in hypersexuality (12% to 8.0% [p=0.047]), gambling (10.7% to 5.3% [p=0.033]) and dopamine dysregulation syndrome (4.7% to 0% [p<0.001]). Remission of impulse control behaviours occurred in 69% of 26 patients, and persisted in the rest, who also had higher levodopa equivalency doses. Patients who developed a new-onset impulse control behaviour during follow-up (n=11) were younger (p=0.042), had less dyskinesia improvement (p≤0.035) and were mostly female (p=0.018). New-onset impulse control behaviours were more common among patients with borderline, schizoid and/or schizotypal traits of personality disorders, and persisted in those with obsessive-compulsive traits.

Comment: Impulse control behaviours can be a devastating complication of PD and its treatment. The effect of STN-DBS on PD patients with impulse control behaviours is not well studied. The encouraging news is that, following STN-DBS, the majority of patients lose their impulse control behaviours (presumably an altered postoperative medication dose is responsible). In the minority with persistent or postoperative *de novo* impulse control behaviours, women, higher levodopa equivalency dose, younger age and personality traits were risk factors.

Reference: J Neurol 2017;264(1):40–8
Abstract

Trajectories of prediagnostic functioning in Parkinson's disease

Authors: Darweesh SKL et al.

Summary: Trajectories of daily functioning and motor and nonmotor features during the 23 years prior to PD diagnosis were researched in this nested case-control analysis of the prospective Rotterdam study. PD was diagnosed in 109 participants during follow-up, with each case matched to ten controls (n=1199). Patients who developed PD more often had problems in instrumental activities of daily functioning during the 7 years before diagnosis, and also more frequently exhibited signs of movement poverty and slowness, tremor and subtle cognitive deficits, and in the past 5 years, they developed additional motor features (including postural imbalance, rigidity and postural abnormalities) and increasingly reported problems in basic daily activities. Patients with PD also increasingly reported symptoms of anxiety and depression and laxative use throughout follow-up, although the differences versus controls only reached statistical significance during the final years before diagnosis.

Comment: Since 1990, the Rotterdam study has followed a huge cohort of older patients (>45 years) who are screened for chronic diseases. Over this time, 109 patients have developed PD. Compared with controls, PD subjects, before diagnosis, had more movement poverty and slowness, tremor and mild cognitive deficits and problems of instrumental activities of daily living. This study confirms subtle motor and nonmotor features precede a diagnosis of PD. It is notable, however, that the average age at PD diagnosis was 78 years, reflecting the very elderly cohort. Hyposmia and REM-sleep behaviour disorder were not evaluated as PD risk factors, reflecting the later discovery of these risk factors for PD.

Reference: Brain 2017;140(2):429–41
Abstract

PREDICT-PD: an online approach to prospectively identify risk indicators of Parkinson's disease

Authors: Noyce AJ et al.

Summary: An evidence-based online algorithm for identifying risk indicators of PD was evaluated in 1323 UK individuals aged 60–80 years without PD; 79% completed yearly assessments. The online tool consisted of a survey and a keyboard-tapping task performed annually for 3 years. Smell tests and genotyping for *GBA* and *LRRK2* mutations were also performed. The results of a systematic review of risk factors and early features of PD were used to develop risk scores, with participants grouped into high- (>15th centile), medium- and low-risk (<85th centile) groups. Outcomes included incident PD and previously defined indicators of increased PD risk ('intermediate markers'), including loss of smell, REM-sleep behaviour disorder and finger-tapping speed. Significant correlations were identified between annual risk scores and intermediate PD markers each year, and between baseline scores and intermediate markers during follow-up. A significant association was seen between incident PD during follow-up and baseline risk score (hazard ratio 4.39 [p=0.045]). *GBA* variants and G2019S *LRRK2* mutations, which were detected in 47 participants, improved the predictive power for incident PD.

Comment: Up to this point, attempts at finding neuroprotectant therapies for PD have been unsuccessful, possibly because PD is not diagnosed early enough. There are increasing numbers of studies attempting to define early 'at risk' patients with 'prediagnosis or prodromal' PD. The authors of this paper have previously performed a meta-analysis of PD risk factors and hence designed an algorithm to stratify risk prospectively as low, medium or high. As well, they could add in genetic risk. The beauty of their approach is that their algorithm can be performed online.

Reference: Mov Disord 2017;32(2):219–26
Abstract

