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CROSS-SECTIONAL ANALYSIS OF INTERRELATIONS BETWEEN FALL-RATE, COGNITIVE MEASURES, UPDRS-SUBSCALES, AND NPI-APATHY IN THE REACT-PD STUDY COHORT

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Introduction

Pirepemat (IRL752) is a cortical enhancer, in development for the treatment of frequent falls in advanced PD. Pharmacologically, it affects a cortico-subcortical circuitry involved in the control of both motor and mental functions including balance and cognition[1]. It has been proposed that weakening of this circuitry is a crucial factor underlying *eg* cognitive impairment and certain motor features including frequent falling in PD[2]. Here we sought to investigate the interrelations between motor and mental symptom domains in a cohort of subjects with advanced PD, cognitive impairment and frequent falling, the REACT-PD study baseline cohort.

Methods

IRL752C003 (NCT05258071) is a double-blind, placebo-controlled, 12-week Phase 2b study investigating the effect of Pirepemat on falls in patients with advanced PD. Outcome measures include fall rate, cognition (MoCA), apathy (NPI), CGI, MDS-UPDRS, tandem walking, and single leg stance test (SLS).

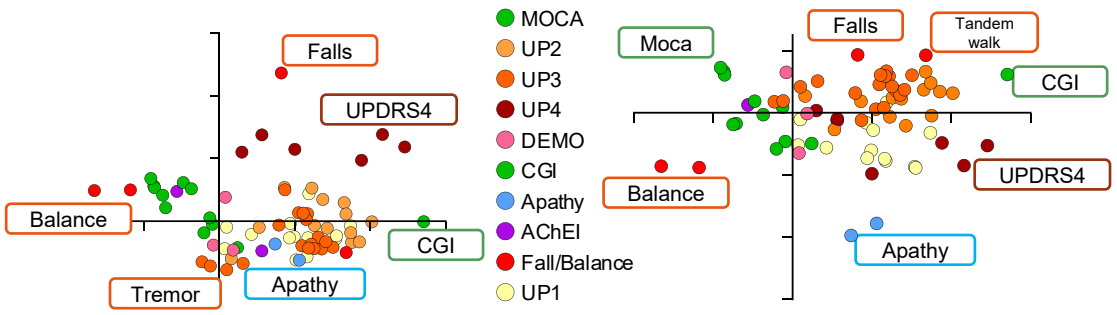
Cross-sectional analysis of different functional domains at baseline was perfomed by principal component analysis (PCA), complemented by orthogonal partial least squares (O-PLS) regression relating fall rates versus other baseline measures. Software: Simca 18.0.1, Sartorius Data Analytics.

Baseline demography & clinical characteristics

	Height (cm)	Weight (kg)	BMI (kg/m²)	MDS-UPDRS 1	MDS-UPDRS 2	MDS-UPDRS 3	MDS-UPDRS 4	Moca	H-Y	NPI-Apathy
n (nmiss)	95 (0)	95 (0)	95 (0)	95 (0)	95 (0)	95 (0)	94 (1)	95 (0)	95 (0)	55 (40)
Mean (SD)	166.8 (9.5)	76 (12.1)	27.3 (4.2)	14.6 (6.2)	22.3 (7)	43 (12.8)	4.7 (3.7)	21.8 (3.3)	3.2 (0.5)	4.5 (3.2)
Median (Min, Max)	169 (145;186)	75.6 (55;109)	26.7 (17.3;39.6)	14 (0;28)	21 (10;41)	42 (17;83)	5 (0;14)	22 (13;30)	3 (2.5;4)	4 (0;12)

Descriptive statistics on baseline data for the IRL752C003 study population (FAS), n= 95.There were 62% males/38% females. Moca: total score. NPI-Apathy: total score (severity*frequency)

Baseline correlation structure – Principal component analysis



Left: Principal component (pc) 1 v2 pc 2. Right: pc 1 vs pc 3

PCA was performed, applying zero mean/UV scaling, and block-scaling in 9 blocks: MoCA, each section of MDS-UPDRS, NPI, SLS/tandem walking, age/sex/ AChE-I comed, and baseline fall-rate. A significant 4 component model was obtained (R^2_X 0.35, Q^2_{cum} 0.11). Loading plots for the first 3 components are shown above. There were no outliers based on t scores (not shown). Overall, MoCA vas inversely correlated to apathy, and to general severity including motor scores (UPDRS parts 1-3) and CGI-S. MoCA was also correlated to balance measures (SLS). Falls were associated with higher scores on MDS-UPDRS 4, complications of therapy. 2nd component shows an inverse correlation between tremor and falls. 3rd component suggests apathy is inversely correlated to falls. Motor severity as such is not clearly associated with baseline fall rate.

Baseline fall rate – underlying factors

O-PLS model of baseline fallrate vs other baseline characteristics. Predictive regression coefficients, centered/scaled, 95% CIs based on cross-validation. Colors: MoCA, CGI, UPDRS 1,2,3,4,Balance, Apathy, Demography, AChE-I.

To specifically explore the impact of demographic/ clinical characteristics on baseline fall rates, O-PLS regression modelling was performed using fall rate as dependent variable, and the other variables as X-block, scaled as above (R^2_Y 0.35, Q^2_{cum} 0.09). Model outcome suggests certain axial motor features (eg speech, posture), along with complications of therapy, MDS-UPDRS part 4, are positively correlated, while tremor is negatively correlated to fall rates.

Conclusions

In this cohort of patients with PD, cognitive impairment and frequent falls, the strongest positive associations with fall rates were observed for MDS-UPDRS part 4, and some specific axial motor symptoms (eg speech). Also, tremor was negative correlated with fall rates. Of note, MDS-UPDRS motor scores in general (part 2, 3), and specific balance measures, were not associated with fall rates. Overall, cognitive performance (MoCA) (especially visuo-spatial, abstraction, orientation) was inversely associated with the degree of apathy, and with overall severity (CGI-S, MDS-UPDRS parts 2,3), but not with falls in this cross-sectional analysis.

[1]Hjorth et al. PMID 32605972 [2]Tait et al, PMID 39920722