

Exploring Expectation Bias in Parkinson's Disease Clinical Trials by Comparing Placebo Arm Progression on MDS-UPDRS to a Natural History Dataset

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INTRODUCTION

- In clinical research, placebo effect (expectation bias) is the beneficial response to an inactive treatment due to the patient's positive belief in that treatment.
- In Parkinson's disease (PD), placebo effects may involve a disease-specific mechanism in addition to the expectation bias:
 - Placebo triggers endogenous dopamine release in the striatum, partially replacing the depleted dopamine in patients with PD.^{1,2}
 - This increase in dopamine has been shown to improve motor performance (e.g., rigidity and bradykinesia).³⁻⁵
- It is hypothesized that progression among PD patients enrolled in placebo-controlled clinical trials vs. non-interventional natural history studies may differ as a result of expectation bias.

OBJECTIVE

To examine baseline characteristics and disease progression of newly diagnosed PD patients enrolled in clinical trials versus natural history.

METHODS

Study participants and data

- Data were obtained from the multicenter natural history cohort Parkinson's progression markers initiative (PPMI) and the critical path for Parkinson's (CPP, data downloaded on September 13, 2023) dataset of clinical trials.
 - PPMI: data from July 1, 2010 to July 1, 2023 for subjects in the PD cohort.
 - CPP: data up to September 13, 2023 for subjects in the placebo group of three disease-modifying treatment (DMT) trials (STEADY PD3, SURE PD3, PASADENA).
- Subjects with confirmed PD within the previous two years, naïve to dopaminergic treatment, with baseline Hoehn and Yahr stage 1 or 2 from both datasets were included in the analysis.
- Patients were censored upon initiation of dopaminergic therapies.

Statistical methods

- Changes in MDS-UPDRS scores over 24-months were compared by examining mean changes from baseline (CFBS) and mean to standard deviation ratios (MSDRs) of CFBS.
 - Mean CFBS and MSDRS were also calculated for individual items at 12-months.
- Difference in mean CFBS and MSDRS between datasets were compared descriptively.
- Time to initiation of dopaminergic therapy was analyzed with the Kaplan-Meier method using a larger subset of data (i.e., all subjects were uncensored for use of therapy).

RESULTS

- A total of 430 and 183 patients met criteria for early-untreated patients with PD from PPMI and CPP. Aggregate baseline characteristics were comparable (Table 1).
- CPP participants improved on Part 1 over the first 12-months (MSDR: -0.21), then reverted to baseline by 24-months (MSDR: 0.01). PPMI participants consistently declined over 24-months (MSDRs of 0.23 and 0.36, at 12- and 24-months, respectively).
- Differences in progression on Part 2 and 3 were less apparent (Figure 1).
- Median time (iqr) in years, from study enrollment to start of dopaminergic therapy was comparable across cohorts: 1.1 (0.5, 2.0) for CPP vs. 0.9 (0.5, 1.8) for PPMI.

Table 1. Demographic and Baseline Characteristics

	PPMI (n=430)	CPP (n=183)
Age in years, mean (SD)	62.8 (9.1)	63.1 (9.4)
Male sex, n (%)	295 (69)	114 (62)
White race, n (%)	400 (93)	169 (92)
Age (in years) at diagnosis, mean (SD)	61.7 (9.1)	62.5 (9.4)
Years since diagnosis, mean (SD)	0.6 (0.5)	0.6 (0.5)
Hoehn and Yahr stage, n (%)		
1	161 (37)	60 (33)
2	269 (63)	123 (67)
MDS-UPDRS Score, Mean (SD)		
Part 1	5.6 (4.3)	5.2 (3.8)
Part 2	5.3 (4.0)	5.0 (4.1)
Part 3 Score (blank/ON state)	20.8 (8.9)	21.4 (8.7)

CPP, Critical Path for Parkinson's; MDS-UPDRS, Modified Unified Parkinson's Disease Rating Scale; PPMI, Parkinson's Progression Markers Initiative; SD, standard deviation.

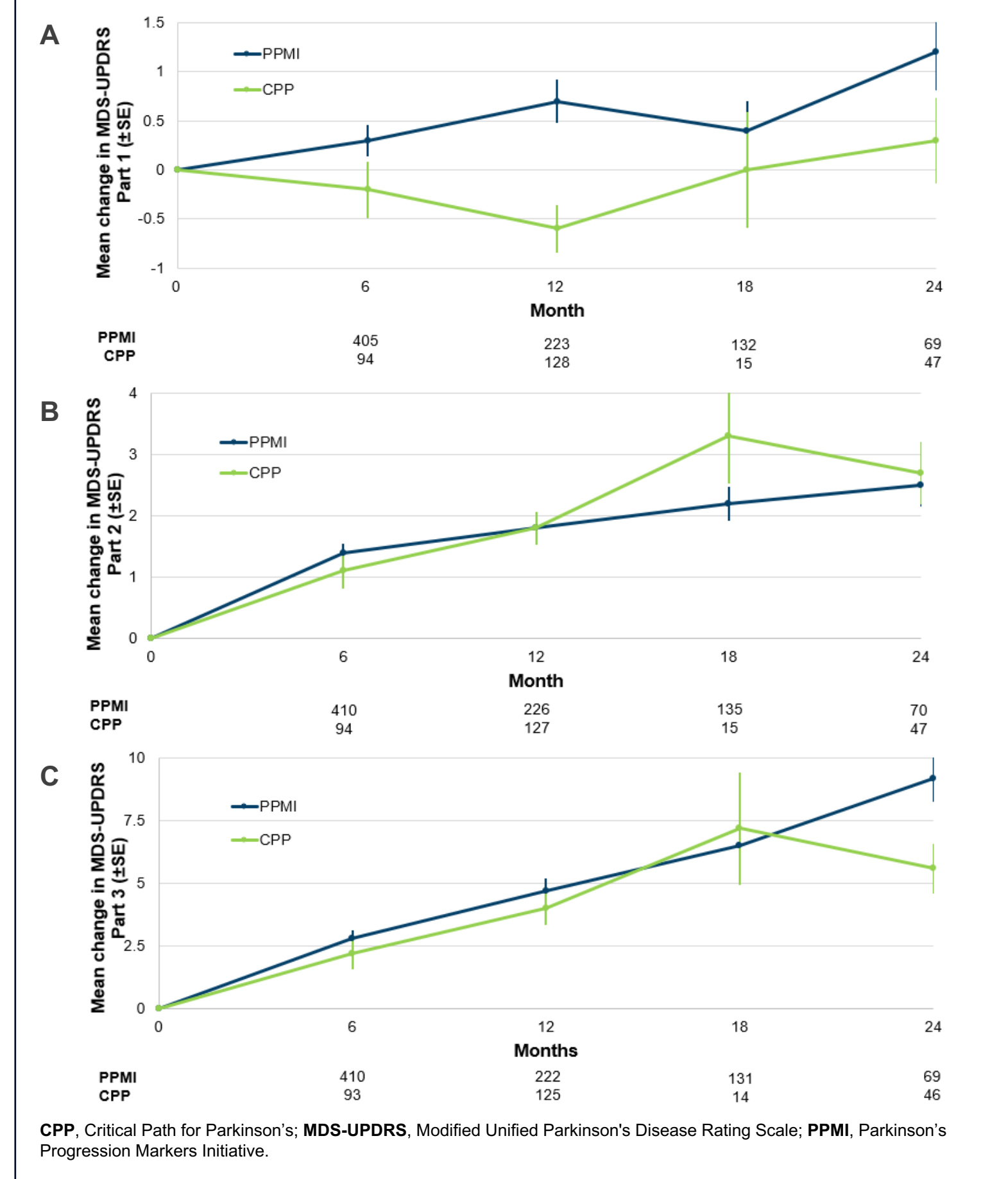
DISCUSSION

- Contrary to prior research, no expectation bias was observed when examining CFB on Parts 2 and 3.
- Given the frequency of assessments (6-month intervals), transient effect on motor symptoms may be missed.
- Studies suggest greater placebo effect in participants with prior experience with PD treatments,³⁻⁵ but our cohorts were naïve to dopaminergic therapies, which may contribute to the lack of placebo effect observed on Parts 2 and 3.
- Expectation bias may be higher with invasive therapies. These trials from CPP utilized oral therapy.

CONCLUSIONS

The natural history and clinical trial placebo arm cohorts were comparable at baseline, progressed similarly on the MDS-UPDRS Part 2 (motor activities of daily living) and Part 3 (motor symptoms), and had similar time to initiation of dopaminergic therapy.

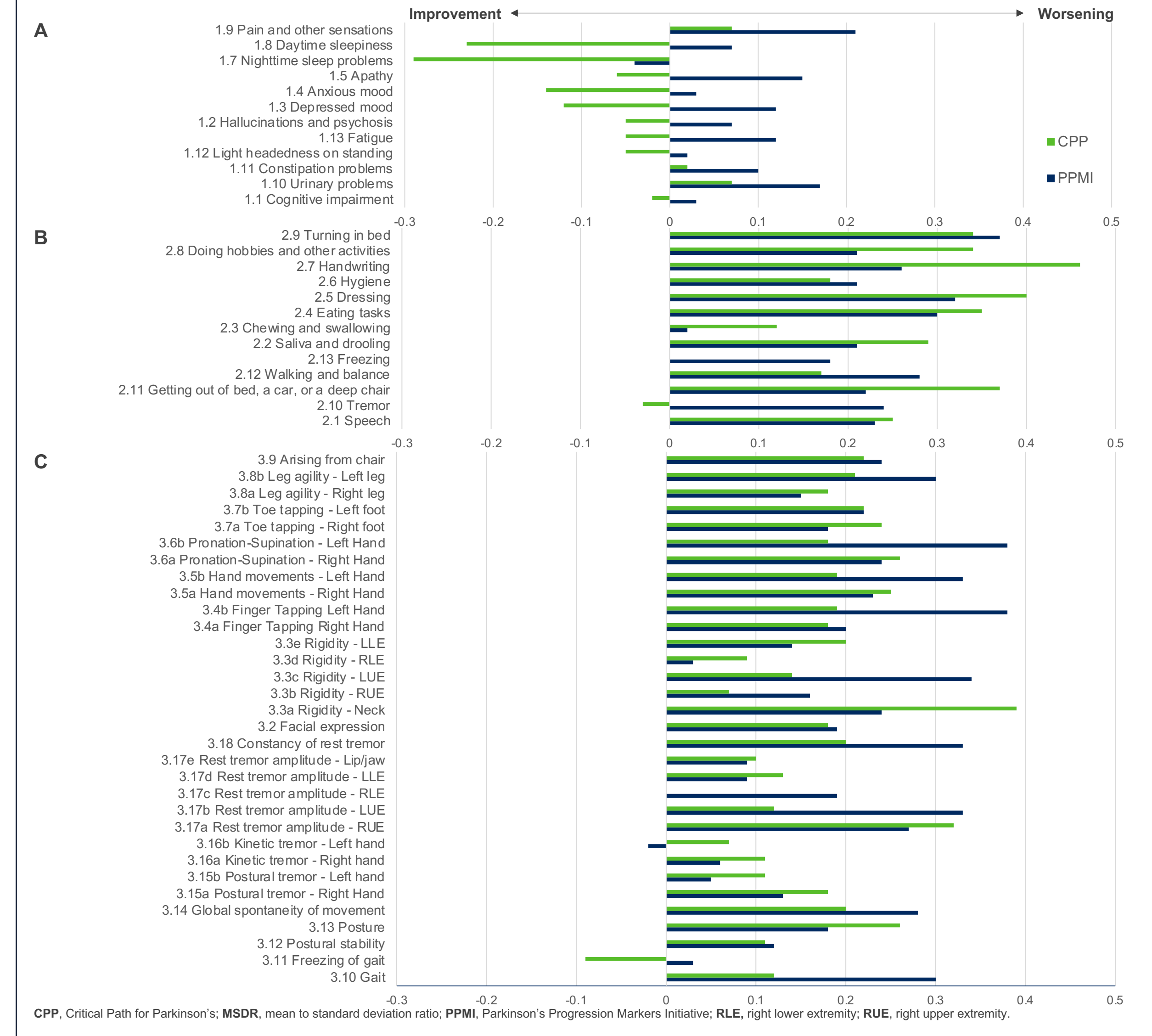
Figure 1. Mean (SE) Change From Baseline on MDS-UPDRS Over 24 Months for (A) Part 1, (B) Part 2, (C) Part 3



CPP, Critical Path for Parkinson's; MDS-UPDRS, Modified Unified Parkinson's Disease Rating Scale; PPMI, Parkinson's Progression Markers Initiative.

- Part 1:** Most items improved in CPP and declined in PPMI (Figure 2).
- Part 2:** Most UPDRS Part 2 items declined at 1-year in both populations, except the tremor item, which demonstrated improvement in CPP. The freezing item was stable in CPP but declined in PPMI (Figure 3).
- Part 3:** Most items demonstrated decline over the 1-year in both cohorts, with a trend for left hand and left upper extremity to show improvements in CPP vs. PPMI.

Figure 2. MSDR Comparison at 1-year for (A) Part 1, (B) Part 2, (C) Part 3



CPP, Critical Path for Parkinson's; MSDR, mean to standard deviation ratio; PPMI, Parkinson's Progression Markers Initiative; RLE, right lower extremity; RUE, right upper extremity.

Potential expectation bias was observed on MDS-UPDRS Part 1 (non-motor experiences of daily living) as the placebo patients improved over the first year on most Part 1 items.

Most research on placebo effect in PD has focused on the impact to motor symptoms given the biochemical basis for this improvement involving endogenous dopamine release. However, in the current analysis, the most clear and sustained signal was seen on MDS-UPDRS Part I non-motor items.

References: 1. Lidstone, S. C. 2014 *Placebo*, 139-147; 2. de la Fuente-Fernández R Science. 2001 Aug 10;293(5532):1164-6; 3. Mercado R *Mov Disord*. 2006 Sep;21(9):1457-61; 4. Goetz CG. *Neurology*. 2000 Feb 8;54(3):710-4; 5. Lidstone SC. *Arch Gen Psychiatry*. 2010 Aug;67(8):857-65

Disclosures: BR, LP, FN, and CDB are or were employees of Broadstreet Health Economics and Outcomes Research at the time study was conducted, which received funding from Biohaven for conduct of this work. JD is an employee of Clintrex Research Corporation and own/options in Revaletio Corporation. LSR is an employee in the Department of Neurology at Johns Hopkins University School of Medicine and received consulting fees from Biohaven. MHP, VC, and GL are employed by and own stock and stock options in Biohaven Pharmaceuticals.

Data Acknowledgements: PPMI: <https://ppmi-info.org>

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2026 American Academy of Neurology (AAN) Annual Meeting
April 18-22, 2026
Chicago and online

