American Academy of Neurology™

Scientific Platform Session: Autonomic Disorders
April 7, 2025; San Diego

NET-inhibition with ampreloxetine, blood pressure, and catecholamines in patients with neurogenic orthostatic hypotension

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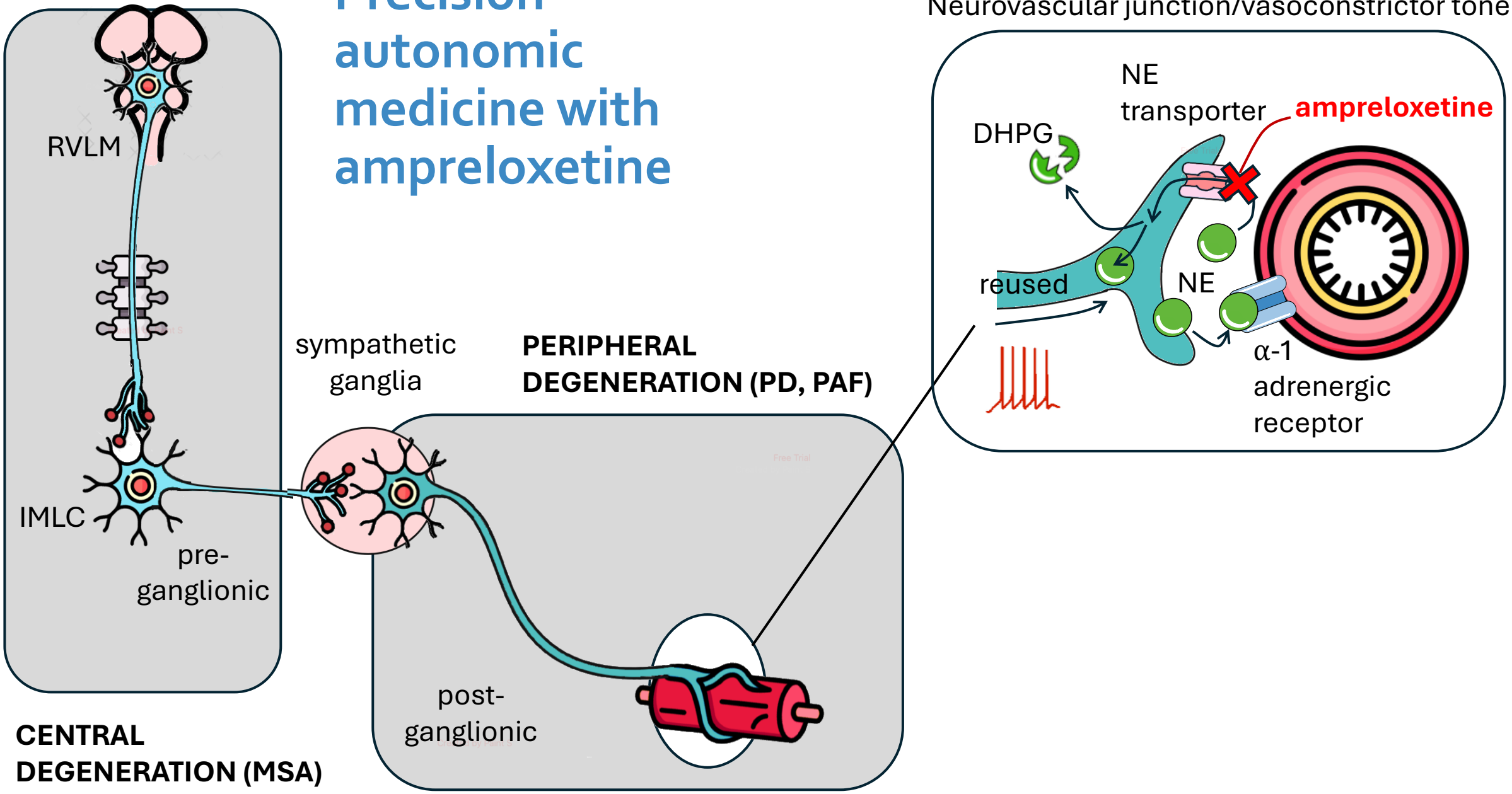
Disclosure: Valeria Iodice has received personal compensation in the range of $10,000-$49,999 for serving as a Consultant for Theravance. The institution of Dr. Iodice has received funding support.

INTRODUCTION

- In most patients with neurogenic orthostatic hypotension (nOH), adequate symptomatic relief is not achieved with available pressor agents.
- No drug has been developed that treats nOH in MSA patients by harnessing residual peripheral autonomic activity
- Ampreloxetine is a novel, long-acting, highly selective norepinephrine reuptake inhibitor being tested as a treatment for nOH in phase III trials.

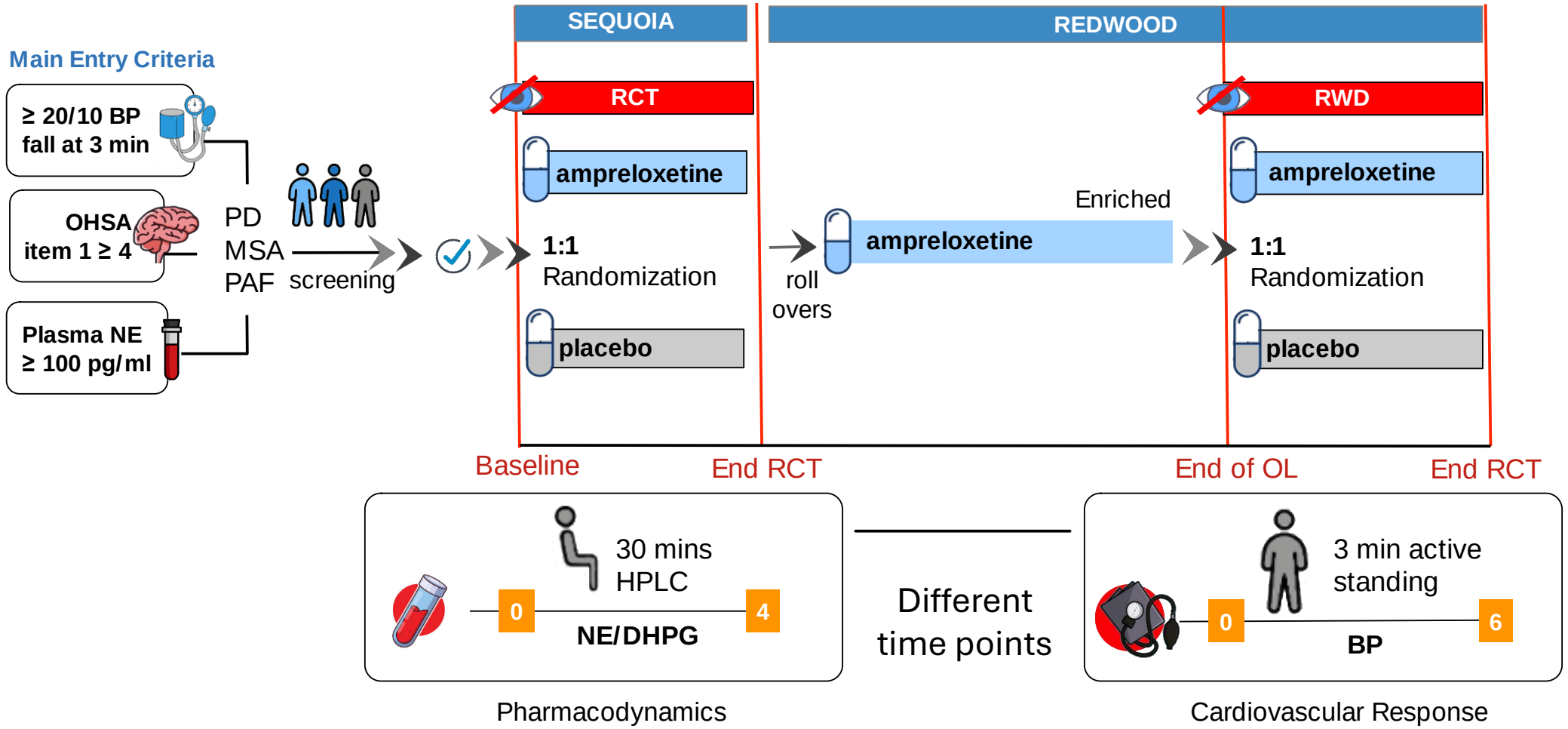
Precision autonomic medicine with ampreloxetine



OBJECTIVE

To determine the impact of ampreloxetine (oral, 10 mg/day) on orthostatic blood pressures (BP) and venous norepinephrine levels in patients with alpha-synucleinopathies.

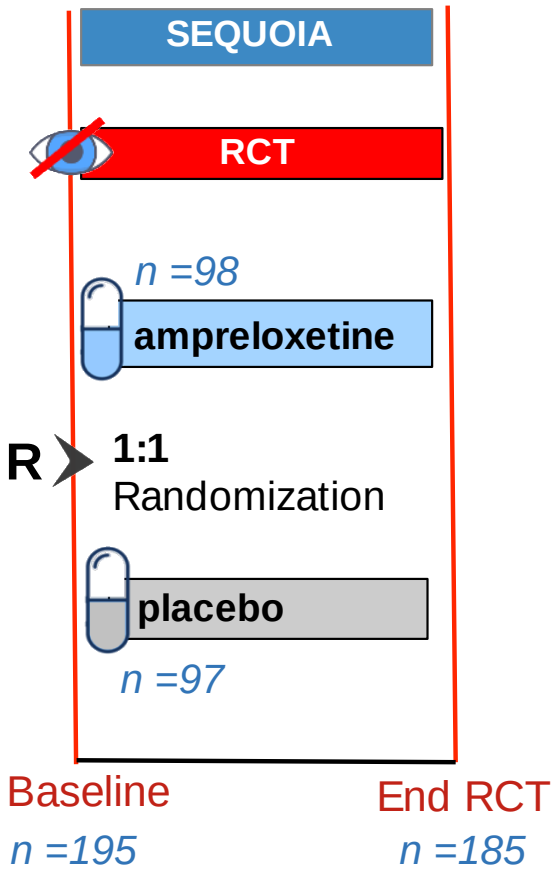
METHODS: Protocol Design and procedures



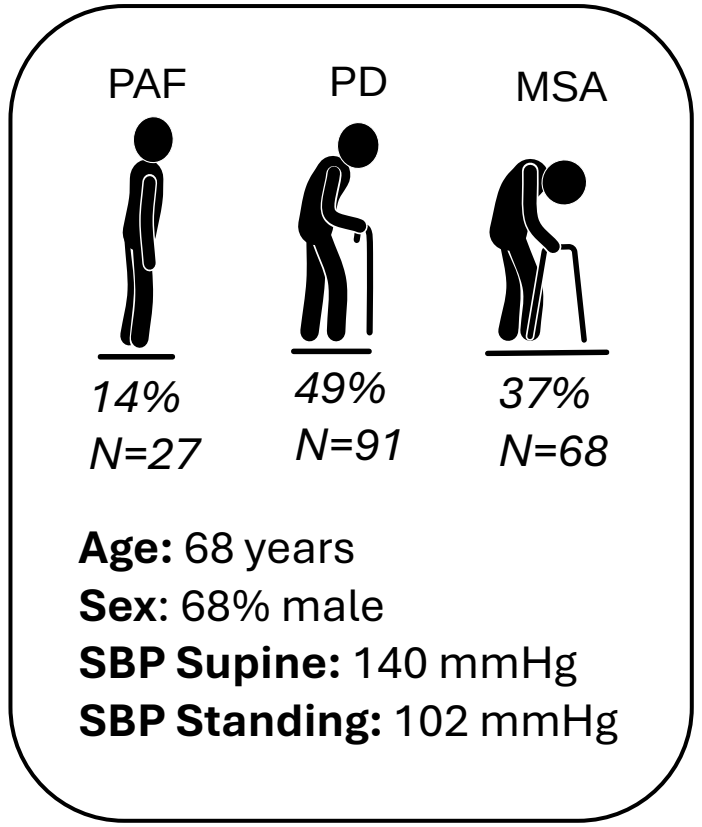
RESULTS: Pharmacodynamics [NE and DHPG]

Subjects that enrolled in 4-week RCT SEQUOIA (NCT # 03750552); and had pharmacodynamic sampling at baseline and week 4

SAMPLE SIZE

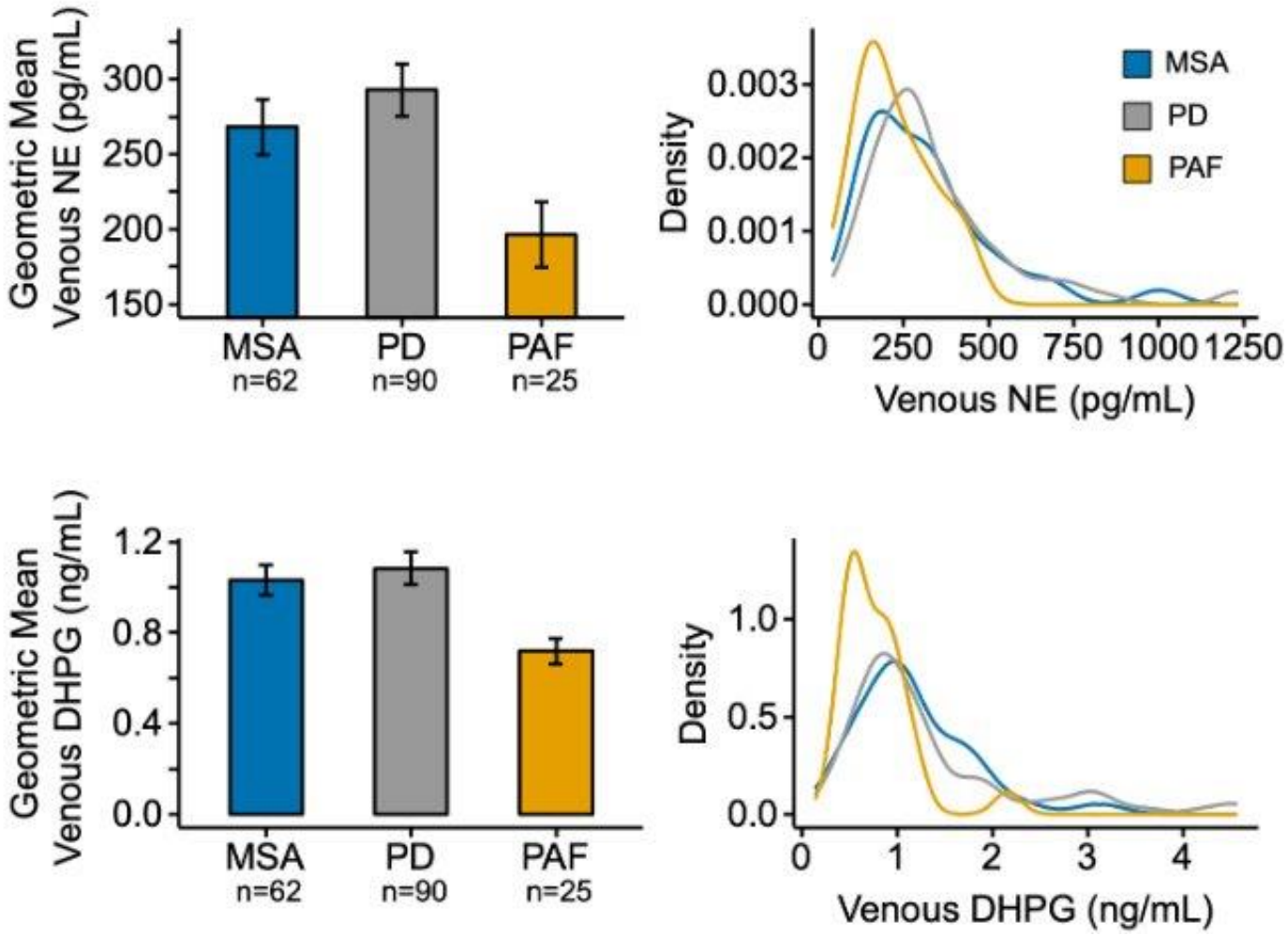


DEMOGRAPHICS and DX SUBTYPE



CATECHOLAMINE PROFILES: Baseline

Pre-treatment NE and DHPG, stratified by underlying diagnostic subgroup



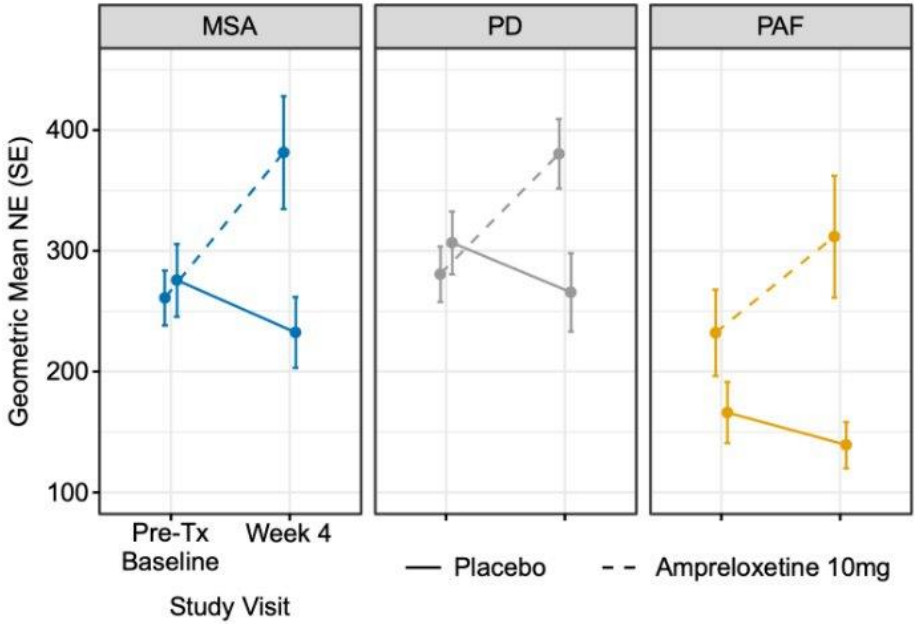
Baseline

- Lowest NE and DHPG in PAF, consistent with severe peripheral sympathetic loss
- Higher and overlapping NE and DHPG levels in MSA and PD consistent with sparing of peripheral sympathetic neurons.

NE PROFILES: Week 4 RCT

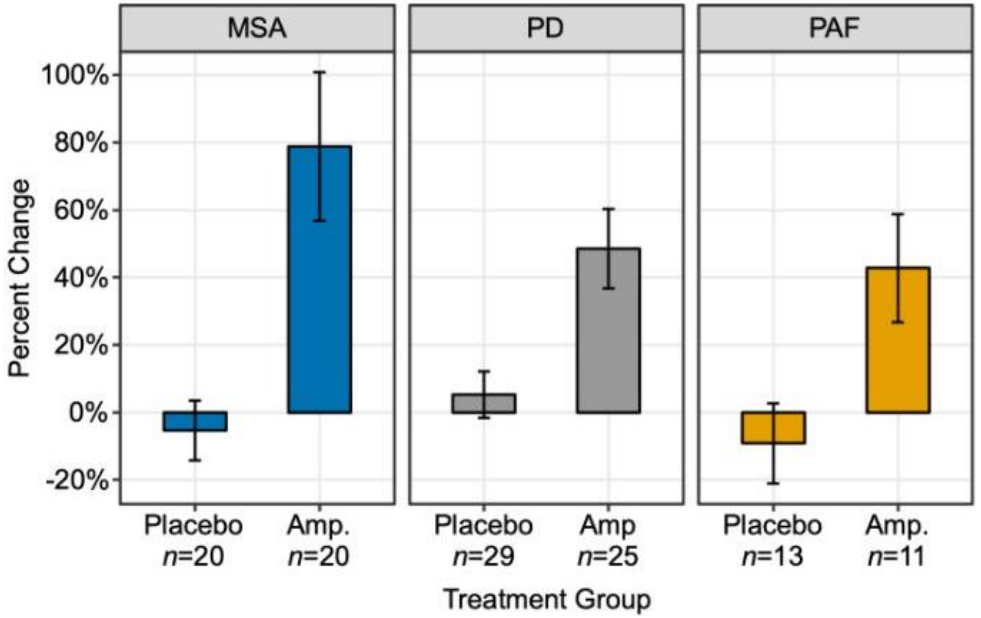
Absolute venous plasma [NE], pre-treatment and at the end of 1:1 randomization, stratified by diagnostic subgroup

Absolute NE levels



- Increase on venous plasma NE levels observed in all 3 diagnostic subgroups
- NE levels most variable in PAF, due to low sample size/more heterogeneity

Percentage change NE levels

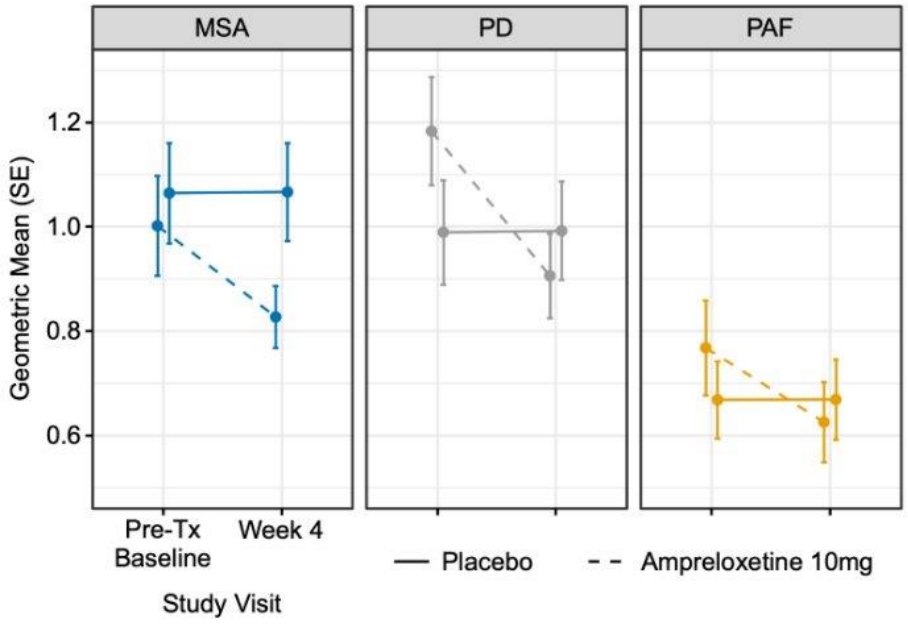


- % NE increase appears to be most robust in patients with MSA
- Consistent with NET-inhibition being ideally suited to patients with a central lesion (i.e., sparing of peripheral autonomic neurons)

DHPG PROFILES: Week 4 RCT

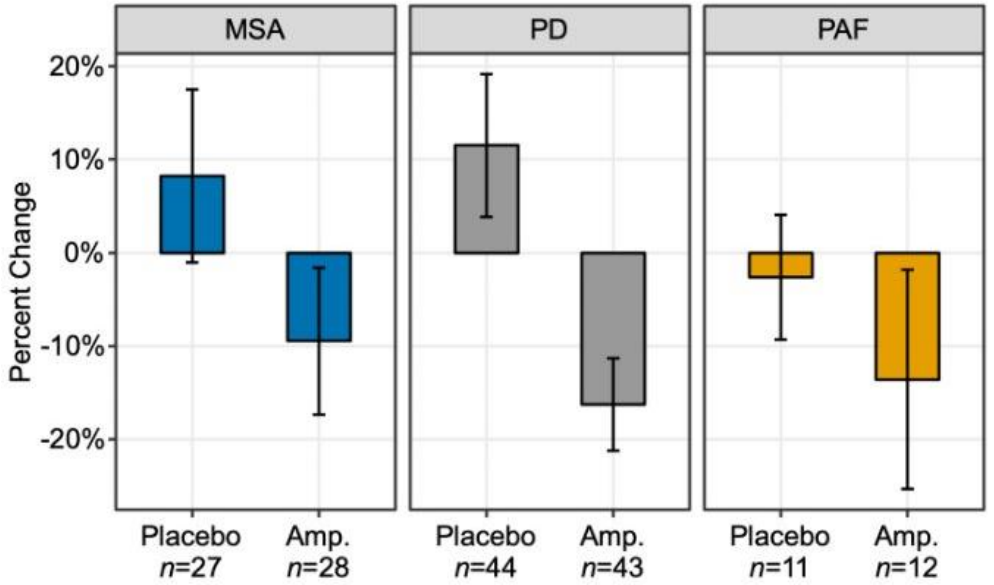
Absolute venous plasma [DHPG], pre-treatment and at the end of 1:1 randomization, stratified by diagnostic subgroup

Absolute DHPG levels



- Less variability at baseline observed in MSA
- Decline in DHPG observed after 4-weeks active treatment, but not on placebo

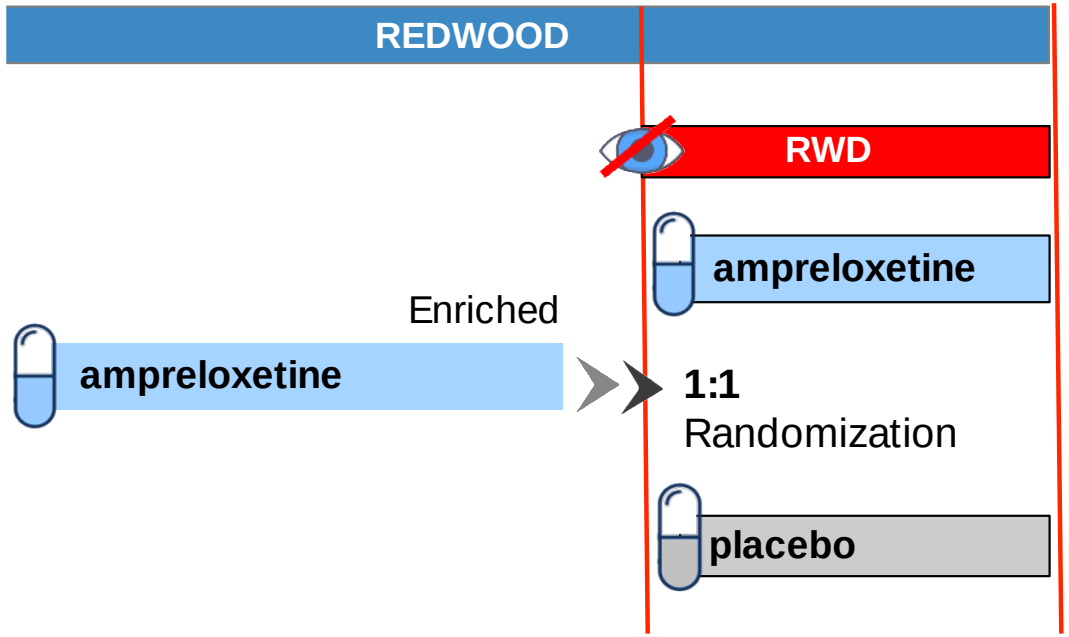
Percentage change DHPG levels



- The reduction in DPHG consistent with lower intraneuronal NE metabolism
- Pharmacodynamic profile of peripheral NE transporter inhibition with ampreloxetine

RESULTS: Autonomic Responses (BP)

Subjects that enrolled in 22-week RWD study REDWOOD (NCT # 03829657); that met open-label enrichment criteria and entered into the 6-week randomized withdrawal phase.



Study Cohort on Entry

15% *53%* *32%*

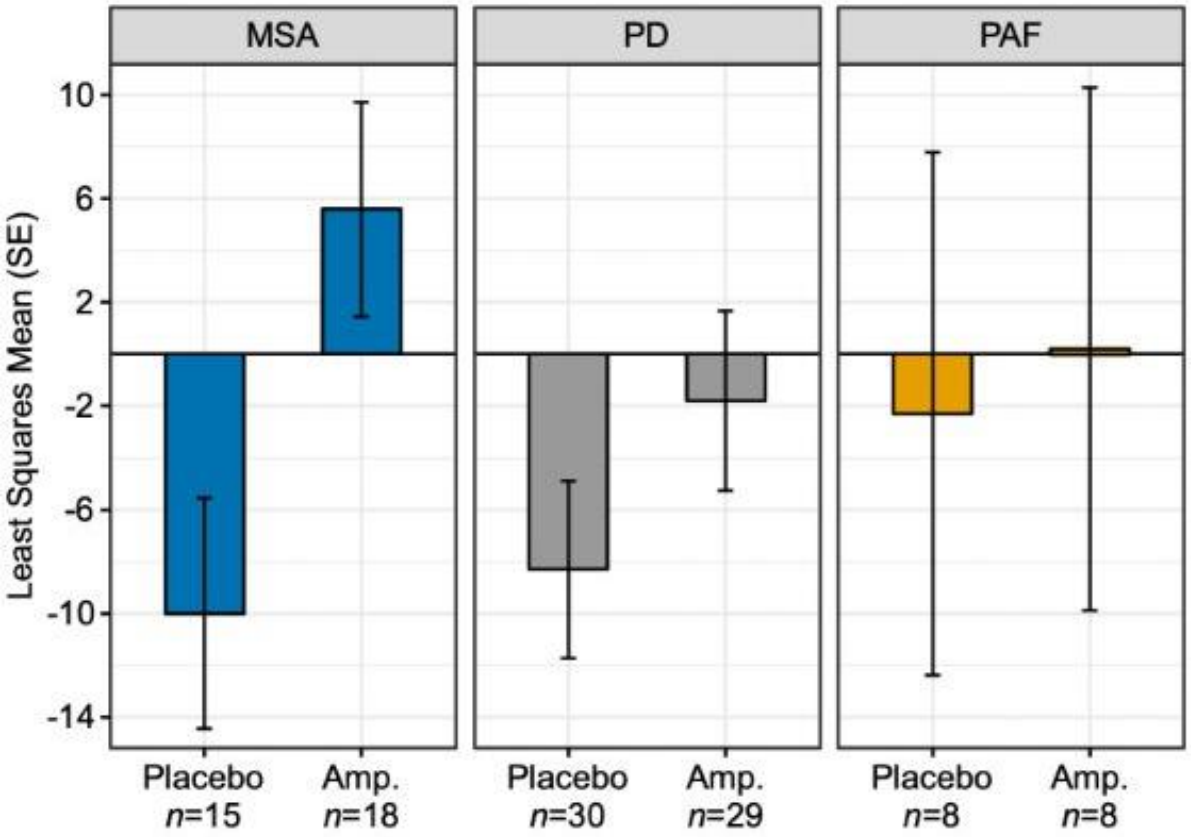
N=31 *N=105* *N=64*

Age: 68 years
Sex: 71% male

SBP Supine: 141 mmHg
SBP Standing: 106 mmHg
NE: 310 pg/ml

RESULTS: Autonomic Responses (BP) Cohort

Subjects that enrolled in 22-week RWD study REDWOOD (NCT # 03829657); that met open-label enrichment criteria and entered into the 6-week randomized withdrawal phase.



Blood pressure change at the end of the randomized withdrawal

- Standing 3-minute systolic BP dropped in the group withdrawn to placebo
- Remained unchanged from the end of the open label in those assigned to remain on ampreloxetine

CONCLUSIONS

- The catecholamine profile observed on ampreloxetine showed target engagement of NE transporter inhibition
- Norepinephrine reuptake inhibition with ampreloxetine resulted in a sustained improvement in orthostatic BP, which was lost in patients that withdrew to placebo.
- This precision therapy is ideally suited to patients with intact peripheral autonomic neurons and uses a re-uptake inhibitor to restore residual nerve function when activated on standing.

ACKNOWLEGDEMENTS

Enrollment Steering Committee
Angelo Antonini, MD
Christopher Gibbons, MD
Ronald Schondorf, MD

Executive Steering Committee
Horacio Kaufmann, MD
Roy Freeman, MD
Valeria Iodice, MD
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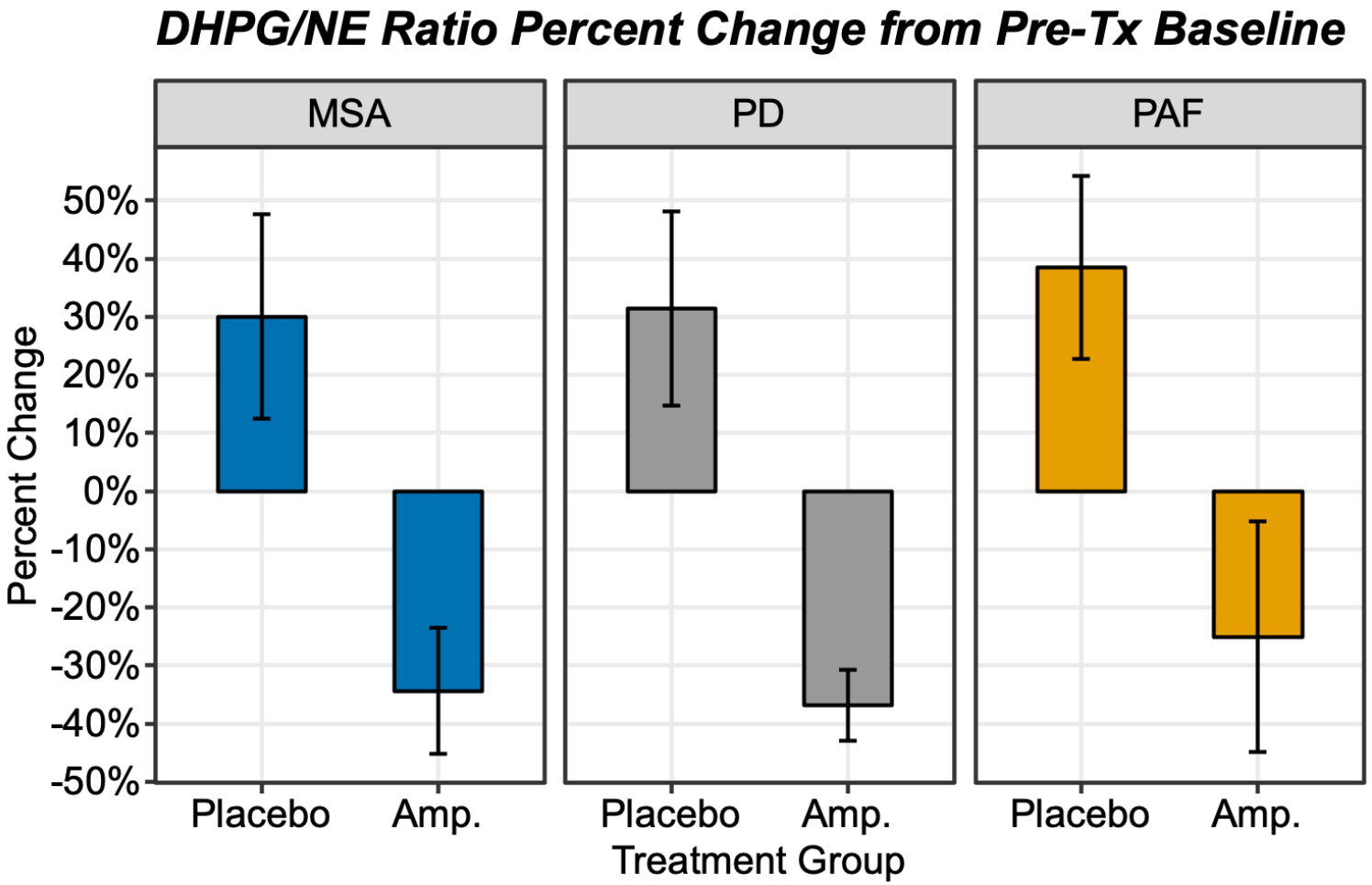
Theravance Biopharma
Aine Miller
Wayne Yates
Roger Koller
Leah O'Brien
Kathan Griscik
Jaime Moy

% change DHPG:NE ratio in the RCT:



DHPG to NE ratio

- Findings consistent with the pharmacodynamic properties of a NE transport inhibitor
- The reduction in DPHG consistent with lower intraneuronal NE metabolism
- The increase in venous NE consistent the enhanced neurovascular transmission