

Noradrenaline treatment of apathy and impulsivity in Progressive Supranuclear Palsy syndromes (NORAPS): A Phase II clinical trial - ISRCTN99462035

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Introduction

Progressive supranuclear palsy (PSP) is a devastating neurodegenerative disorder with limited evidence-based treatment options. Apathy and impulsivity are common and burdensome features. Apathy and impulsivity often coincide and correlate *positively* with each other.

Apathy and impulsivity correlate with the degree of destruction of the locus coeruleus, the brain’s principal source of noradrenaline.

NORAPS tested the hypothesis that restoring noradrenaline levels by noradrenaline reuptake inhibition is safe, well tolerated and improves apathy and impulsivity.

Background

The locus coeruleus in the dorsal pons is the main source of noradrenaline in the central nervous system. The locus coeruleus degenerates early and severely in PSP, with up to 90% (mean 50%) loss of noradrenergic cells at *post-mortem* studies.

Experimental single-dose studies have shown atomoxetine to have favourable effects against measures of apathy and impulsivity.

Methods

NORAPS was an investigator led Phase II clinical trial, using atomoxetine 40mg OD PO in liquid form *versus* matched liquid placebo, for eight weeks each. It was a double-blind, placebo-controlled crossover study with 2 weeks washout between treatment phases.

Co-primary endpoints were (i) safety and tolerability of atomoxetine in PSP; (ii) challenging behaviours subscale of the revised Cambridge Behavioural Inventory. Secondary endpoints include measures of cognition, behaviour, quality of life, anxiety, depression and response inhibition in relation to drug.

Participants had a diagnosis of Probable or Possible Progressive Supranuclear Palsy. Clinical assessments were performed at baseline screening visit, and at the beginning and end of each 8-week treatment block.

Pertinent exclusion criteria were concomitant noradrenergic medication use (e.g. SNRI / MAO-inhibitors), history of ischaemic heart disease, atrial fibrillation, and recent malignancy (excluding locally isolated prostate cancer). Carer and participant questionnaires were answered at the beginning and end of both treatment blocks, with a final study visit 4 weeks after last dose, for additional safety data.

81 participants were randomized, with 74 receiving at least one dose of investigational medicinal product. 68 participants has PSP-Richardson Syndrome phenotype.

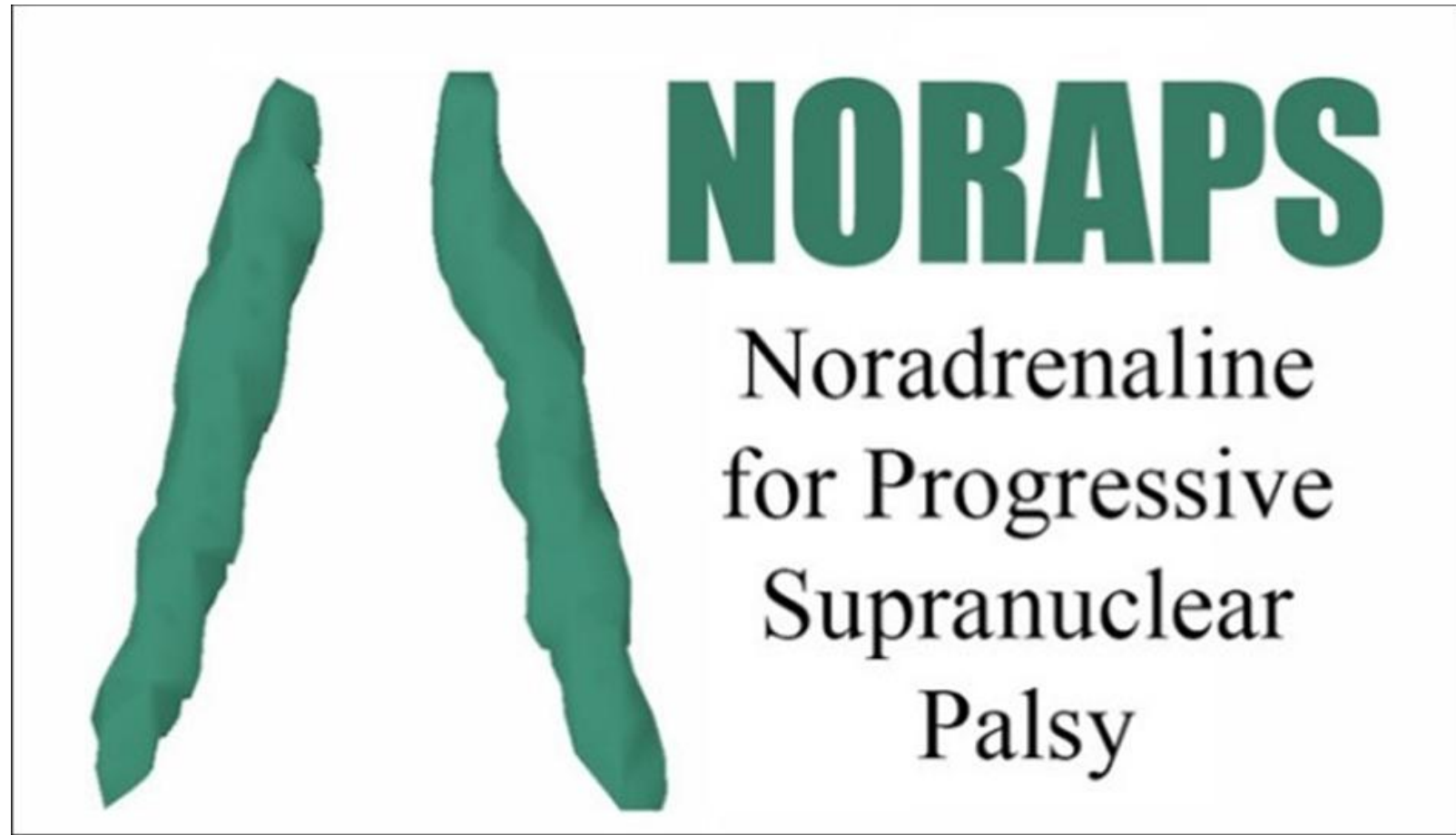
Recruitment completed in summer 2025.

Hypothesis

We sought to establish that Atomoxetine was safe and well tolerated in patients with Progressive Supranuclear Palsy, and also effective at treating the symptoms of Apathy and Impulsivity in PSP, versus placebo

Primary Outcome

	Treatment		Treatment Effect	
	Placebo	Active	Unadjusted Estimate	Adjusted Estimate ¹
CBI-R-I (Full Imputation) (N=80)				
Treatment Start	22.5 (16.0)	22.2 (14.8)		
Treatment End	22.2 (15.7)	20.4 (15.2)	1.78 (-0.35 , 3.90) p = 0.101	1.73 (-0.38 , 3.83) p = 0.108



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Secondary Outcomes

	Treatment		Treatment Effect
	Placebo	Atomoxetine	Adjusted Estimate ¹
CBI-R Total			
Treatment Start	53.2 (30.1)	47.3 (25.4)	
Treatment End	48.7 (30.4)	45.5 (29.4)	3.96 (-9.16 , 7.46) p = 0.832 N=20
CamQUAIT Apathy Score			
Treatment Start	52.2 (10.0)	52.4 (9.8)	
Treatment End	52.3 (9.9)	52.3 (9.9)	- 0.08 (-1.33 , 1.17) p = 0.893 N=55
PSP Quality of Life - Carer			
Treatment Start	33.4 (21.2)	33.9 (21.0)	
Treatment End	35.5 (22.4)	33.7 (22.2)	0.96 (-2.28 , 4.20) p = 0.556 N=58
CAARS – Patient Reported			
Treatment Start	23.8 (13.8)	24.2 (14.2)	
Treatment End	25.6 (14.7)	23.0 (14.7)	-1.16 (-5.00 , 2.68) p = 0.548 N=67
CAARS – Carer Reported			
Treatment Start	22.0 (15.9)	22.2 (14.8)	
Treatment End	20.3 (16.1)	22.4 (18.0)	-1.96 (-6.64 , 2.72) p = 0.406 N=67
HADS Anxiety			
Treatment Start	4.55 (3.81)	4.25 (3.18)	
Treatment End	4.82 (3.55)	4.40 (3.95)	0.04 (-0.70 , 0.78) p = 0.916 N=63
HADS Depression			
Treatment Start	7.92 (4.43)	8.19 (4.43)	
Treatment End	7.93 (4.43)	7.66 (4.46)	0.09 (-0.83 , 1.02) p = 0.838 N=56
RBANS Total Score			
Treatment Start	69.1 (14.7)	71.5 (12.4)	
Treatment End	72.9 (12.7)	72.9 (16.5)	- 1.37 (-3.57 , 0.84) p = 0.220 N=56

Recruitment

	Placebo-Atomoxetine (N=41)	Atomoxetine-Placebo (N=40)
Age	73.3 (6.23)	72.4 (6.00)
BMI	26.7 (4.29)	28.6 (4.92)
Years of Education	12.7 (3.26)	12.8 (2.77)
Sex:		
Male	22 (53.7%)	27 (67.5%)
Female	19 (46.3%)	13 (32.5%)
Ethnicity:		
White	40 (97.6%)	39 (97.5%)
Non-white	1 (2.4%)	1 (2.5%)
Handedness:		
Left	3 (7.3%)	3 (7.5%)
Right	37 (90.2%)	37 (92.5%)
Ambidextrous	1 (2.4%)	0

Exploratory Outcomes

	Treatment		Treatment Effect
	Placebo	Atomoxetine	Adjusted Estimate ¹
MoCA Score			
Treatment Start	21.4 (4.6)	21.9 (3.8)	
Treatment End	22.0 (4.7)	21.5 (4.8)	0.35 (-0.45 , 1.15) p = 0.388 N=60
Frontal Assessment Battery			
Treatment Start	36.5 (9.3)	36.2 (9.8)	
Treatment End	37.3 (9.9)	37.8 (9.5)	0.28 (-0.41 , 0.98) p = 0.412 N=60
PSP Rating Scale			
Treatment Start	36.5 (9.3)	36.2 (9.8)	
Treatment End	37.3 (9.9)	37.8 (9.5)	- 0.88 (-2.20 , 0.45) p = 0.190 N=65

Discussion and Future Direction

NORAPS unfortunately did not show efficacy against any of it’s primary, secondary or provisional exploratory outcomes using 40mg of Atomoxetine in PSP.

Safety data is being analysed, but no preliminary signal is suggestive of a significant difference in adverse events between treatment groups.

Further exploratory work is underway using blood-based biomarkers of neurodegeneration and neuroinflammation to test if atomoxetine imparts an effect on the pathobiology of PSP.

1: Adjusted for baseline difference in outcome and treatment sequence.