Author, Year. Study Type	Population	Primary Objective	Comparison groups	Cognitive Testing	Orthostatic Testing	Other Testing	Results	Remarks	OH & CI Related?

Supplementary Table 1: A Summary of the Direct Evidence Papers Reporting on the Association between Orthostatic Hypotension and Cognitive Impairment in Alpha-Synucleinopathies

Author, Year. Study Type	Population	Primary Objective	Comparison groups	Cognitive Testing	Orthostatic Testing	Other Testing	Results	Remarks	OH & CI Related?
Peralta, et al. 2007. Cross-Sectional	18 patients (unreported genders) with PD and PDD (PDD = MMSE <24) matched for age and disease duration	To assess the frequency and severity of OH in patients with PD and PDD and to assess the effect of OH on attention and word fluency cognitive tests.	10 PD: mean age 74.1 y, mean disease duration 6.4 y, mean H&Y 2.1. 8 PDD: mean age 77.3 y, mean disease duration 7.8 y, mean H&Y 2.9.	MMSE plus tests of verbal memory, CERAD and executive function.	Tilt table testing: 10 minutes supine then 10 minutes tilted to 60 degrees. OH defined as drop of sBP >/= 20 mmHg and/or dBP >/= 10 mmHg.	Cognitive testing (attention and verbal fluency) done supine and tilted at 60 degrees.	PDD had higher H&Y stage and performed worse on cognitive tests. OH found in 5 PDD, 2 PD (p=0.088). Mean sBP drop greater in PDD than PD (p<0.05). Tilt produced a decrease in attention scores in PDD patients. There was a significant correlation between orthostatic changes and attention scores in PDD but no influence on word fluency tasks observed.	In a small study of PD patients with and without dementia, orthostatic drop in systolic blood pressure was more severe in PDD compared to PD without dementia. OH exacerbated attentional deficits although, this may have been due to distraction from head tilt or fatigue during the procedure. Did not account for dopaminergic medications.	Yes
Idiaquez, et al. 2007. Cross-Sectional	40 PD patients (26 M) and 30 (18M) age-matched controls. Excluded: early (within 4 years) dementia, fluctuations, visual hallucinations, neuroleptic sensitivity and patients with probable MSA.	To test the hypothesis that CI would be more severe in patients with OH than in patients without OH.	11 PD patients had dementia: 7 M, mean age 76.4 y, mean PD duration 10.5 y, mean H&Y 3.4. 29 non-demented PD patients: 19 M, mean age 66.2 y, mean PD duration 9.9 y, mean H&Y 2.6.	MMSE, FAB.	Postural BP: BP measured after 30 minutes supine then after 1, 2, 5 and 10 minutes of standing. OH defined as >/= 20 mmHg drop in sBP.	SCOPA-AUT for autonomic symptoms. Heart rate response to deep breathing (HRDB).Post prandial HoTN. Blessed scale (ADLs) and Cornell scale (depression).	PDD patients were older and at higher H&Y stage than PD patients. No difference in incidences of OH, PPH, mean HRDB between PD and PDD patients. Cardiovascular symptoms on SCOPA-AUT was higher for PDD than PD without dementia.	In a small study of patients with PD, OH and cognitive impairment were not correlated, although cognitive testing included only MMSE and FAB. Cardiovascular symptoms were more prominent in PDD than PD patiehts without dementia. All tests done 12 hours off dopaminergic medications.	No
Hohler, et al. 2012. Cross-Sectional	44 PD patients (27 M). Ages and disease duration unreported	To investigate motor and cognitive function and to test the hypothesis that motor and cognitive function would be more impaired in PD patients with OH compared to those without OH.	17 patients had OH 27 did not have OH	MMSE and functional independence measure (FIM) as a measurement of disability - has 5 cognitive items.	Postural BP: BP in seated position, then recorded within in 1-3 minutes of standing. OH defined as drop of >/= 20 mmHg in sBP or 10 mmHg in dBP at any time when upright.	Motor features: Two minute walking test, timed up and go test, Berg balance scale (BBS), Finger tapping test.	No differences in gender, disease severity, educational level in patients with compared to without OH. Patients with OH had lower cognitive FIM score and lower MMSE. Motor FIM and BBS were also worse in the OH+ group.	PD patients with OH had worse cognitive function, but also worse motor, walking and balance compared to PD patients without OH. The study did not control for mean age between groups and did not account for dopaminergic medications.	Yes
Bae, et al. 2014. Cross-Sectional	45 drug-naive Korean PD patients (17 M)	To determine the relationship between CI and OH in drug-naive and non-demented PD patients.	18 patients with OH: 8 M, mean age 61.3 y, mean PD duration 11.48 y, mean H&Y 2. 27 patients without OH: 9 M, mean age 65.5 y, mean PD duration 16.1 m, mean H&Y 2.	Seoul Neuropsych Screening Battery. Domains tested included attention, language, calculation, visuospatial, memory and frontal-executive.	Tilt table test: 10 minutes supine then tilt to 60 degrees. BP measured at 1, 3 and 5 minutes. OH defined as drop of >/= 20 mmHg in sBP or 10 mmHg in DBP at any time when upright.	N/A	Performance on all cognitive domains were similar between OH+ and OH- with and without OH with the exception of the recognition test of verbal memory which was worse in the OH+ group. There were non-significant trends where the OH+ group performed worse on the recognition test of visual memory and discrimination tasks of recognition.	In a small sample of drug-naive PD patients, verbal memory recognition performance was worse in patients with OH compared to those without OH. Blood pressures measured off dopaminergic medications.	Yes
Pilleri et al. 2013. Cross-Sectional	48 PD patients (26 M) with disease duration under 5 years and absence of atypical features. Patients with DBS excluded.	To compare cognitive function in PD patients with and without OH and to assess the contribution of cerebrovascular lesions on MRI.	23 patients with OH: 13 M, mean age 64.96 y, mean PD duration 11.48 y, mean H&Y 2.65. 25 patients without OH: 13 M, mean age 65.6 y, mean PD duration 11.76 y, mean H&Y 2.76.	MMSE and FAB. Domains tested included working memory, sustained attention, attention shifting, verbal fluency, verbal memory and visuospatial functions.	Tilt table test: BP measured after 10 minutes rest, then 60 degrees upright for 3 minutes. OH defined as drop of >/= 20 mmHg in sBP or 10 mmHg in DBP.	Section 1 of non-motor symptoms scale administered for presence of symptoms of OH. Evaluation for supine hypertension. MRI for evaluations of white matter hyperintensities (ranked w/ SRS score).	Age, disease duration and H&Y stage were similar between OH+ and OH- groups. Only 56% of OH+ patients had symptoms of OH. 9 OH+ patients had SH. MMSE similar in OH- and OH+. OH patients had lower scores in attention, Corsi test, RAVLT delayed recall. SH did not contribute to cognitive dysfunction. No difference in SRS scores.	PD patients with OH had impairment of attention, visuospatial working memory, verbal delayed recall compared to those without OH. THere was no difference in cerebrovascular white matter burden between OH+ and OH- patients with PD. Levodopa dose equivalents were similar between groups.	Yes
Anang, et al. 2014. Prospective - followed up mean 4.4 y	80 PD patients (51 M), without dementia at baseline. Mean age 66.2, mean disease duration 5.7 y.	To assess a large number of potential risk factors, specifically non-motor features, for dementia in a prospective cohort of patients with PD.	27 patients developed dementia:22 M, mean age 70.5 y, mean PD duration 6.02 y, mean H&Y 2.8. 53 patients did not develop dementia: 29 M, mean age 63.6 y, mean PD duration 5.4 y, mean H&Y 2.3.	Tests of executive function and attention, memory (verbal fluency, episodic verbal learning and memory) and visuospatial domains.	Postural BP: BP measured supine and after 1 minute standing. No definition for OH listed.	Symptoms of OH, urinary dysfunction and constipation assessed w/ UMSARS questionnaire.	PD patients with dementia were older at baseline and more likely to be male. There was no difference in disease duration or disease stage between groups at baseline. Risk factors for developing dementia included baseline MCI, RBD, higher baseline BP, abnormal colour vision, proportion of gait involvement, falls and freezing. OH was strongly associated with dementia risk (OR = 1.84 per 10 mm Hg) and a systolic drop in BP of >10 mm Hg increased the odds of developing dementia by 84%.	OH, among other variables, predict the development of dementia in PD. Did not evaluate baseline cognitive reserve, history of head injury, non-parkinsonian medication use, family history of dementia. Did not account for dopaminergic medications.	Yes
Kim, et al. 2012. Cross-Sectional	87 Korean patients with early PD (35 M). None on antiparkinsonian medications. Patients with signs of MRI were related to atypical PD or secondary parkinsonism were excluded. 32 patients had OH.	To assess if cognitive abnormalities or white matter abnormalities on MRI were related to neurocardiovascular autonomic dysfunction in patients with PD.	25 patients with normal cognition: 14 M, mean age 63.4 y, mean PD duration 1.8 y, mean H&Y 1.4. 48 patients with MCI: 16 M, mean age 70, mean PD duration 1.9 y, mean H&Y 1.7. 14 patients PDD: 5 M, mean age 66.2 y, mean PD duration 1.6 y, mean H&Y 2.1.	MMSE, CDR (clinical dementia rating scale), Seoul Neuropsych Screening battery (assessed for attention, language, praxis, Gerstmann syndrome, visuospatial function, verbal and visual memory, frontal / executive function).	Tilt table test: 30 minutes supine then tilted 60 degrees for 20 minutes. BP measured 5 minutes before and at 1, 3, 5, 10, 15, 20 minutes during tilt. OH defined as drop of >/= 20 mmHg in sBP or 10 mmHg in DBP.	24-hour ambulatory BP monitoring, supine HTN defined as = >150/90 mmHg. Also 24-hr ambulatory BP and HR. MRI for WMH and CHIPS scale (cholinergic pathways hyper intensities scale)	Gender and disease duration between groups according to cognitive status were similar. Mean age was higher in MCI group and H&Y stage was higher in PDD group. OH was correlated with verbal immediate and delayed memory and CHIPS scores. There was a trend towards higher CHIPS in patients with OH. Patents w/ dementia had marked reductions in BP during tilt: 71% of PDD patients had OH while 20% of patients with normal cognition had OH. SH was also correlated with dementia and CHIPS scores. Patients with OH + SH had more severe CI and higher CHIPS scores than those with neither OH nor SH. Mean CHIPS score was higher in patients with dementia than with normal cognition or MCI.	In patients with early PD, cognitive impairment was associated with OH and SH. Both OH and SH were more prevalent in PDD than PD patients with normal cognition. Both cognitive impairment and neurocirculatory abnormalities were associated with increased CHIPS scores, a measure of white matter hyperintensities. No patients were on dopaminergic medications.	Yes
Allcock, et al. 2004. Cross-Sectional	89 PD patients (51 M).	To determine the frequency and clinical associations (including cognitive impairment) of OH in patients with PD.	42 patients with OH: mean age 72.6 y 45 patients without OH: mean age 68.2 y	MMSE	Postural BP: BP measured after 10 minutes rest then after 3 minutes standing. OH defined as a drop in sBP of >/= 20 mm Hg or to <90 mmHg.	Geriatric Depression Score, Montgomery and Asberg Depression Rating Scale	Patients with OH were older than those without OH. There was no difference in disease duration or severity in OH groups (values not reported). There was no difference in the rating of depression between groups. There was no difference in MMSE scores in patients with and without OH.	There was no difference in MMSE scores in PD patients with and without OH. Accounted for levodopa dose equivalents between groups.	No
Allcock, et al. 2006.	159 PD patients (97 M)	To describe and compare clinical features of patients with PD with and without OH.	80 patients with OH: 56 M, mean age 72.1 y, median PD duration 3 y, median UPDRS 19.	MMSE	Postural BP: measured after 10 minutes supine, then standing at 1,2,3 minutes. OH defined	29-point autonomic symptoms questionnaire (gastrointestinal, genitourinary,	Patients with OH patients were older and more likely to be male than those without OH. There was no difference in disease duration or severity between groups. Patients with OH were taking higher levodopa dose equivalent than those	There was no difference in MMSE scores in PD patients with and without OH. Patients with OH were taking higher levodopa dose equivalent than	

Cross-Sectional			**79 patients without OH**: 41 M, mean age 69.1 y, median PD duration 5 y, median 17.		as drop of >/= 20 mmHg in sBP or 10 mmHg in DBP.	cardiovascular, thermoregulatory symptoms). COMPASS (composite autonomic symptom scale).	without OH. **There was no difference in MMSE in patients with and without OH.**	those without OH.	**No**
Allcock, et al. 2006.	**175 PD patients (109 M)** recruited from community based PD cohort and hospital PD clinic. **PD patients w/ dementia included.**	To compare the neuropsychological profile of PD patients with OH compared with those without OH and determine if PD patients with OH have evidence of more diffuse Lewy body pathology.	**87 patients with OH**: 63 M, mean age 72.4 y, median PD duration 3.5 y, median UPDRS 18.5.	**MMSE** and tests from **Cognitive Drug Research computerized assessment** (attention, executive function, working memory, verbal memory and visual memory domains assessed).	**Postural BP:** Measured after 10 minutes supine then 3 minutes standing. OH defined as drop of >/= 20 mmHg in sBP or sBP of <90 mmHg.	N/A	PD patients with OH were older and more likely male than those without OH. Comparing OH+ to OH- patients, there was no difference in duration of PD, UPDRS, co-morbid vascular disease or medications that cause cognitive impairment. The OH+ group had higher total levodopa equivalent dose. **MMSE scores were not different between OH+ and OH- groups.** Adjusted for age and dose of dopamine, **OH+ patients were less accurate in digit vigilance test and visual episodic memory worse.** These differences persisted when patients with MMSE <24 excluded.	PD patients with OH performed worse on on digit vigilance and picture recognition tasks than those without OH, although there was no difference in MMSE scores between these groups. Patients with OH were older and on a higher total levodopa dose.	
Cross-Sectional			**88 patients without OH**: 46 M, mean age 69.2 y, median PD duration 5 y, median UPDRS 17.						**Yes**

ADLs = activities of daily living, BP = blood pressure, sBP = systolic blood pressure, dBP = diastolic blood pressure, CERAD = consortium to Establish a Registry for Alzheimer's Disease, CHIPS = Cholinergic Pathways Hyperintensities Scale, DBS = deep brain stimulation, CI = cognitive impairment, F = female, FAB = frontal assessment battery, H&Y = Hoen and Yahr Stage, HoTN = hypotension, HTN = hypertension, M = male, MCI = mild cognitive impairment, MMSE = Mini mental state exam, OH = orthostatic hypotension, OH+ = has OH, OH- = does not have OH, PD = Parkinson's Disease, PDD = Parkinson's Disease Dementia, RAVLT = Rey Auditory Verbal Learning Test, RBD = Rapid eye movement Sleep Behaviour Disorder, SCOPA-AUT = Scales for Outcomes in Parkinson's Disease - Autonomic, SCOPA-COG = Scales for Outcomes in Parkinson's Disease - Cognitive, SH = supine hypertension, SRS = Scheltens rating scale, UMSARS = Unified Multiple System Atrophy Rating Scale, UPDRS = Unified Parkinson's Disease Rating Scale.