Conclusions Results show sustained treatment effect and continued benefit with AVAL beyond the PAP, and stabilization of treatment effect after switching from ALGLU to AVAL over 97 weeks, supporting long-term maintenance of clinically meaningful outcomes with AVAL.
Funding Sanofi

2287 THE IMPACT OF SLEEP ON THE PROGRESSION OF PARKINSON'S DISEASE: A MENDELIAN RANDOMIZATION STUDY

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10.1136/bmjno-2022-ANZAN.80

Introduction Sleep disturbance is common in Parkinson's disease (PD) and significantly impacts quality of life. Although often considered a sequelae of PD, there is emerging evidence that sleep disturbance may itself play a causal role in neurodegeneration via altered clearance of pathological proteins. Whether sleep disturbance affects the pathological progression of PD is unknown.
Methods To elucidate the causality between sleep disorders and progression of PD, we performed two sample Mendelian randomization analysis using genetic variants identified from GWAS databases for sleep variables including insomnia, sleep duration, chronotype, napping and daytime sleepiness. Outcome measures were derived from a large collective GWAS of PD progression(N=4093 cases) including the Unified Parkinson's disease rating scale (UPDRS total and UPDRS- III), motor fluctuations, Age of onset of PD, Mini-mental state examination (MMSE) and Montreal Cognitive Assessment (MOCA). The robustness of results was examined using conventional Mendelian randomization sensitivity analyses.
Results Genetic liability to increased sleep duration was associated with a lower rate of progression of motor symptoms in PD using UPDRS-III score. Meanwhile insomnia was associated with increased rate of motor progression of PD. Predisposition to daytime sleep was associated with lower rates of progression of cognitive decline in PD measured using MMSE. No robust relationships were determined between markers of progression and chronotype or dayime napping. Statistical measures showed significant pleiotropy for the relationships identified.
Conclusion Sleep-related variables may have a deterministic role in the clinical progression in Parkinson's disease and may represent a modifiable target for altering the trajectory of neurodegeneration.

2289 DYNAMIC NETWORK IMPAIRMENTS UNDERLIE COGNITIVE FLUCTUATIONS IN LEWY BODY DEMENTIA

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10.1136/bmjno-2022-ANZAN.81

Objective Cognitive fluctuations are a core clinical feature of Dementia with Lewy bodies (DLB), and although common and disabling, their pathophysiology is poorly understood. This work aimed to identify novel functional network signatures of cognitive fluctuations and investigate their underlying neurobiology by relating them to neuromodulatory systems.
Methods Patients with DLB and age-matched controls were assessed on both subjective and objective measures of fluctuations and attention. Resting state dynamic functional magnetic resonance imaging was used to identify the temporal and topological signatures of cognitive fluctuations. Abnormal patterns of activation were mapped onto established gene expression atlases to determine associations with specific neuromodulators.
Results DLB patients displayed more stationary brain-state configurations relative controls. This signature of reduced temporal variability correlated significantly with fluctuation-related measures using a sustained attention task (response time variability and drift rate). Topologically, patients with DLB demonstrated a less integrated (more segregated) functional network architecture compared to the control group. Regions of reduced integration were observed across dorsal and ventral attention, sensorimotor, visual, cingulo-opercular and cingulo-parietal networks. Relatively segregated networks correlated positively with subjective and objective measures of fluctuations. Regions of reduced integration and unstable regional assignments were significantly related to the pattern of expression of specific classes of noradrenergic and cholinergic receptors across the cerebral cortex.
Conclusions Cognitive fluctuations in DLB are related to specific dynamic functional network impairments that are linked to the noradrenergic and cholinergic systems. Such systems may be viable targets of future therapies.

2291 PLASMA NEUROFILAMENT LIGHT CHAIN AND CLINICAL DIAGNOSIS IN FRONTOTEMPORAL DEMENTIA SYNDROMES

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10.1136/bmjno-2022-ANZAN.82

Objective To study plasma NfL levels in people with frontotemporal dementia (FTD) syndromes and determine if plasma NfL can distinguish between FTD syndromes and FTD phenocopy, whom are difficult to clinically distinguish from bvFTD.
Methods Plasma NfL was estimated using two independent Quanterix Simoa machines (a HD-X and SR-X). Participants referred to a tertiary national outpatient cognitive service were characterised into bvFTD, slowly progressive bvFTD (slow progressor), phFTD, motor neuron disease with FTD (FTD-MND), semantic variant FTD (svFTD) and non-fluent variant FTD (nfvFTD). Statistical comparisons were performed using non-parametric tests.
Results Fifty participants, mean age 67.2 (standard deviation 8.4) years and mean follow-up duration of 3.6 (2.4) years were analysed, and 49 patients had a final diagnosis of an