NeeuroCycle to be an accessible, safe, and cost-effective way for older adults to maintain or improve cognitive health, which is beneficial for ageing societies.

P18: Differences in cognitive decline in amnestic mild cognitive impairment due to primary age-related tauopathy and Alzheimer's disease

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Objectives: Primary age-related tauopathy (PART) is associated with cognitive impairment, characterized by the presence of neurofibrillary tangles composed of tau protein, independent of amyloid plaque deposition. In this study, we examined the differences in neuropsychological assessments between PART and Alzheimer's disease (AD) over a three-year follow-up period in patients with amnestic mild cognitive impairment (amnestic MCI).

Methods: Ten patients (mean age = 75.9; SD = 7.0; Global Clinical Dementia Rating Scale = 0 or 0.5) were recruited from Memory Clinic at Keio University Hospital. They were classified into two groups of five patients with amnestic MCI or subjective cognitive impairment due to either PART (amyloid-/tau+) or AD (amyloid+/tau+) based on the results of [18 F]PM-PBB3 and [18F]Florbetaben Positron Emission Tomography imaging scanning. A battery of neuropsychological tests: Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale (ADAS), Logical memory test of Wechsler Memory Scale–Revised, Word fluency, Trail Making Test (TMT), was administered at baseline (the first visit) and after three years.

Results: All patients remained as MCI (Global CDR = 0.5) at three-year follow-up. Although ADAS score was deteriorated more in AD than PART group at three-year follow-up ($p < 0.05$), PART and AD groups did not differ in overall cognitive abilities including memory. However, in PART group, the TMT A & B completion time tended to be prolonged compared to AD group ($p = 0.98$). On the other hand, TMT B/A indicated as executive function was indifferent in both groups.

Conclusions: Patterns of cognitive decline trajectory differed between PART and AD in amnestic MCI, suggesting a difference in the neuropathological course leading to progression to AD. PART may show greater decline in visuospatial attention compared to AD. It implies that PART has distinct neuropathological and clinical features compared to AD.

P19: Design of ADEPT-2, a phase 3, parallel group study to evaluate xanomeline and trospium as a treatment for psychosis associated with Alzheimer's disease dementia

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Background: Psychosis represents a major unmet medical need in patients with Alzheimer's disease (AD) dementia. With no approved medications for AD dementia psychosis (ADP), current treatment relies on off-label uses of antipsychotics with limited efficacy and significant safety concerns. Xanomeline is an M1/M4 preferring

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muscarinic receptor agonist that has previously been shown to have antipsychotic effects in subjects with AD (Bodick et al., 1997). While xanomeline had promising efficacy for potentially treating psychosis in AD, cholinergic adverse events limited further clinical development of xanomeline. Xanomeline and trospium is an investigational treatment that combines xanomeline with trospium, an FDA-approved non- specific muscarinic receptor antagonist. Unlike xanomeline, trospium does not measurably cross the blood-brain barrier, providing a mechanism to mitigate peripheral cholinergic effects of xanomeline while maintaining its muscarinic receptor agonist activities in the brain.

Methods: ADEPT-2 trial is a phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the safety and efficacy of xanomeline and trospium for the treatment of ADP. Subjects aged 55-90 years with moderate to severe psychosis associated with mild to severe AD dementia will be enrolled into the study. Eligible subjects will be randomized to receive either xanomeline and trospium or placebo in a double-blinded manner for 12 weeks and subjects who complete the study will be eligible to participate in a one-year, open-label safety extension study.

Results: The primary efficacy endpoint of the study is change from baseline to end of Week 12 in the Neuropsychiatric Inventory-Clinical (NPI-C): Hallucinations and Delusions (H+D) score and the key secondary efficacy endpoint is change from baseline to end of Week 12 in the Cohen- Mansfield Agitation Inventory (CMAI). The safety endpoints include the evaluation of safety and tolerability of xanomeline and trospium compared with placebo in subjects with ADP. The study started in 2023 and will enroll approximately 360 subjects with psychosis associated with AD dementia.

Conclusions: ADEPT-2 is designed to assess the safety and efficacy of xanomeline and trospium for the treatment of psychosis in patients with AD dementia. If ADEPT-2 is successful, xanomeline and trospium have the potential to be the first in a new class of pharmacologic treatment for AD psychosis based on muscarinic receptor agonism.

P20: Perceived cognitive failures, symptoms of bipolar disorder, and psychological well-being

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Introduction: Young and older adults with bipolar disorder (BD) commonly present with cognitive deficits. Many also report subjective or perceived cognitive failures.

Objectives: For this study, we identified four distinct clusters of adults with BD on the basis of both BD symptoms (depression and hypo/mania) and perceived cognitive errors (i.e., forgetfulness, distractibility, false triggering). We hypothesized that participants reporting more BD symptoms and cognitive errors would report lower psychological well-being (i.e., self-efficacy, life scheme, life satisfaction).

Methods: From the BADAS (Bipolar Affective Disorder and older Adults) Study, we identified 281 adults with BD (*M* = 44.27 years of age, range 19–81), recruited via micro-targeted social media advertising (vs. mass marketing to general samples). All clusters significantly differed across all grouping variables except symptoms of hypo/mania due to low frequency.

Results: Across clusters, perceived cognitive failures and BD symptoms increased in lockstep; that is, those reporting more cognitive errors also reported significantly higher symptoms of both depression and hypo/mania. As hypothesized, they also reported significantly lower psychological well-being.

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