(IG: n = 12) and a control group (CG: n = 12). Eighteen participants completed the study after 24 months. Data of one and two-year follow-up revealed a stable significant intervention effect on the primary outcome ADAS-cog in the IG compared to controls (p = .024). On secondary outcomes, significant improvement in mood (Montgomery Asberg Depression Rating Scale, MADRS) disappeared after the end of the 6-month intervention. Significant effects on immediate memory (Repeatable Battery for the Assessment of Neuropsychological Status, RBANS) became apparent at the end of the intervention phase and remained stable to the end of the study (p = .019). Only participants of the CG (6 of 24) converted into AD during the 24-months study period. **Conclusions:** Benefits of our 6-month multicomponent cognitive intervention on global cognitive status and on immediate memory appear to be preserved beyond the time of intervention over extended follow-up periods. Furthermore, participation in the cognitive intervention may be able to delay conversion to AD for at least 2 years. Findings in a small sample of subjects encourage the use of the intervention in larger scales studies to confirm these effects.

O3-07-06 METHODOLOGICAL ISSUES IN CLINICAL TRIALS OF ALZHEIMER'S DISEASE

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Background: The methodology of conducting CNS clinical trials is vital to their success and failure. The high rate of failure in other areas of CNS drug development had led to some disinvestment by pharmaceutical companies in certain areas of CNS drug development. There lessons to be learnt both from recent clinical trials in Alzheimer's disease and other areas of CNS drug development to guide the design and methodology of future trials. **Methods:** A review was undertaken od both failed and successful clinical trial programs in Alzheimer's disease and other CNS disorders, to glean lessons that could guide future development programs. Factors were divided into sponsor factors, site factors and research subject factors. **Results:** Certain sponsor, site, and research factors were seen to impact study success. Methodological factors such as study design, subject recruitment, selection, validity of diagnosis, quality of outcome measure assessments were seen to have an effect and will be discussed. **Conclusions:** Future clinical trial programs should be designed to take into account methodological lessons learnt from both previous Alzheimer's and other CNS clinical trial programs.

O3-07-07 POTENTIAL ALZHEIMER'S TREATMENTS GM-CSF AND G-CSF IMPROVE COGNITION IN CANCER PATIENTS

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Background: Rheumatoid Arthritis (RA) patients appear to be about 8-fold less likely to develop Alzheimer's disease (AD) than the general population. While it has been commonly assumed that RA patients' usage of non-steroidal anti-inflammatory drugs (NSAIDs) helped prevent the onset and progression of AD, NSAID clinical trials have proven unsuccessful in AD patients. We sought instead to identify intrinsic factors within RA pathogenesis itself might underlie RA's protective effect. For example, several colony stimulating factors that activate phagocytic and other immune cells are released during RA that we surmised might stimulate bone marrow macrophages to enter the brain arereduce amyloid and/or promote neurogenesis, neurite outgrowth, or angiogenesis. **Methods:** We investigated the effect on a mouse model of AD of injecting both bolus amounts of each of three colony-stimulating factors-macrophage-, granulocyte- and granulocyte-macrophage colony stimulating factor-into the one side of the brain or of GM-CSF subcutaneously daily over three weeks. Pathology and/or behavior of the mice were examined. We also analyzed the archived results of a human trial of the standard FDA approved dosage of recombinant human GM-CSF and G-CSF in bone marrow transplant patients, whose cognitive scores in a battery of neuropsychological test were assessed at baseline, 6 months, and 12 months. **Results:** In the AD mice experiments, we found that GM-CSF reduced amyloid deposition and completely reversed cognitive decline. GM-CSF was more efficacious than the related G-CSF. In the human study, the data indicated that combined administration of GM-CSF and G-CSF significantly improved cognition in a variety of cancer patients receiving HCT, with the inclusion of GM-CSF being more efficacious than G-CSF alone. The improvement in cognition was strongest in the memory domain at 6 months and extended also to the executive domain by 12 months, thereby providing human data on the efficacy of GM-CSF for this new cognitive indication. A pilot trial to test the safety and efficacy or GM-CSF in mild to moderate Alzheimer's disease patients is planned, and preliminary findings, if any, will be reported. **Conclusions:** These preclinical and clinical results suggest that GM-CSF administration may represent a new approach to AD therapy based on the stimulation of bone marrow macrophages to enter the brain, differentiate into microglia and inhibit the AD pathogenic pathway.

O3-07-08 TESAMORELIN, A GROWTH HORMONE-RELEASING HORMONE ANALOGUE, IMPROVES COGNITIVE FUNCTION IN MCI AND HEALTHY AGING: RESULTS OF A RANDOMIZED CONTROLLED TRIAL

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Background: Animal and clinical studies show that the somatotrophic axis, which modulates circulating levels of growth hormone, growth hormone-releasing hormone (GHRH), and insulin-like growth factor I (IGF-I), has potent effects on brain function. Age- and disease-related changes in this axis set the stage for targeted therapeutic interventions to improve cognitive function. In an earlier pilot study, we demonstrated that six months of GHRH treatment had positive effects on cognition for healthy older men and women. These results also provided preliminary evidence that similar benefits might be observed for adults with mild cognitive impairment (MCI). **Methods:** Using a double-blind, randomized, placebo-controlled study design, 124 subjects (55-87 yrs old, 59% women) received subcutaneous injections of tesamorelin, a stabilized analogue of human GHRH (1 mg/d, provided by Theratechnologies Inc.) or placebo 30 min before bedtime for 20 weeks. Sixty subjects (n=27 amnestic MCI) in the tesamorelin group and 64 subjects (n=28 amnestic MCI) in the placebo group completed the study. Prior to enrollment, study candidates received a neuropsychological assessment with diagnostic adjudication and medical screening. At baseline and week 20, cognitive function was assessed including tests of executive function and episodic memory, oral glucose tolerance tests were performed, and blood was collected for assay of IGF-I, glucose, insulin, and lipids. **Results:** Tesamorelin significantly increased plasma levels of IGF-I over baseline ($p < 0.0001$) but remained within physiological range. Both for healthy older adults and adults with MCI, tesamorelin improved performance on executive function tests of response inhibition (p=0.009, Stroop Color Word Interference test) and set-shifting (p=0.01, Task Switching), and a statistical trend also suggested tesamorelin-related improvements in working memory (p=0.07, Self-ordered Pointing Test). On tests of memory, tesamorelin significantly improved delayed verbal recall for adults with MCI but not for healthy older adults (MANOVA tx*dx interaction, p=0.05). General cognitive status (MMSE), visual memory, word fluency, and processing speed were not affected by treatment. **Conclusions:** This study is the first to demonstrate that short-term tesamorelin administration improves executive function for healthy and memory-impaired older adults, and has a favorable effect on verbal memory for adults with MCI who are at high risk of progression to Alzheimer's dementia.