placebo group over the ERG 10mg group, but no discernible difference from the ERG 25mg group. Within-group effects comparing to baseline revealed significant improvements in cognitive domains including executive function, complex attention, cognitive flexibility, and verbal memory for both the ERG 10mg and ERG 25mg groups (all $p < .05$). For secondary outcomes, a significant improvement in Getting to Sleep scores for the ERG 25mg group (LSEQ, $p=.04$), and an overall treatment effect favouring better Prospective Memory scores for the ERG 25mg group was observed. Both the ERG 10mg and 25mg groups showed dose-dependent increases in blood-plasma Ergothioneine levels and decreases in liver enzyme markers (AST and ALT; all $p < .05$).

Conclusions: This study demonstrated the effects of short-term Ergothioneine supplementation on primary and secondary health outcomes including cognitive function, sleep, and prospective memory. Increased blood-plasma Ergothioneine levels and reduced liver enzyme markers suggest additional potential benefits. Future studies should measure mechanistic markers and consider longer interventions to assess cognitive impacts.

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PTFS07-01-24 Warfarin Treatment Is Associated With Lower Post-mortem Brain Vitamin K Concentrations

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Objectives: Menaquinone 4 (MK4) is the primary form of vitamin K in the brain. Brain MK4 concentrations were significantly lower in mice treated with Warfarin, a vitamin K antagonist. Further, higher brain MK4 concentrations have been positively correlated with cognitive function. However, it is not known if brain MK4 levels are influenced by warfarin treatment in humans. To address this, we compared post-mortem brain MK4 concentrations in older adults treated with warfarin to older adults not treated with warfarin.

Methods: We utilized data obtained from 380 autopsied participants (76% female, mean (SD) age 92 (6 years) of the Rush Memory and Aging Project (MAP) in whom MK4 was measured in the mid-frontal and temporal cortices ((MTC) averaged for statistical analysis), anterior watershed (AWS), and cerebellum. Linear regression was used to compare (natural log) brain MK4 concentrations between those treated and not treated with warfarin (based on self-report), adjusted for age, sex, and cognitive diagnosis at death (categorized as no cognitive impairment, mild cognitive impairment (MCI), or dementia). The association of warfarin use prior to death with cognitive diagnosis at death was evaluated using logistic regression, adjusted for age, sex, education, and apoE4 status.

Results: Warfarin users (n=73, median (IQR) duration of warfarin use = 218 (142-292) days) had 68-79% lower brain MK4 concentrations in all measured regions including the mean across all regions compared to non-Warfarin users (β= -1.352, -1.357, -1.538, -1.140; all p< .001, fully adjusted). Participants diagnosed with dementia prior to death had significantly lower MK4 concentrations in the MTC and AWS (β=-0.278 (p=0.04), β= -0.389(p=0.01), respectively). However, the odds of having MCI or dementia, compared to no cognitive impairment, at death did not differ between warfarin users and non-users (odds ratio (95% confidence interval) MCI = 0.82 (0.41, 1.62), dementia = 1.05(0.57, 1.93)).

Conclusions: These findings suggest that Warfarin treatment influences MK4 concentrations in the human brain. MK4 concentrations were lower in Warfarin users compared to non-users, however the odds for dementia did not differ with warfarin use due to lower risk of stroke and other cerebrovascular (CV) sequelae due to atrial fibrillation and other CV risk factors.

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PTFS07-02-24 Seizure Amelioration Effect of Omega-3 EPA and DHA Fatty Acid Supplementation on Patients With Drug Resistant Epilepsy: A Scoping Review Using the GOED Clinical Study Database

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Objectives: 70% of patients with epilepsy are successfully treated with one or a combination of anti-seizure medications (ASMs). The latter 30%, do not respond to ASMs and continue to have uncontrollable seizures. They are known to have drug-resistant epilepsy (DRE). There is an unmet need for non-pharmacological treatment options to be considered. The objective of this scoping review is to assess the seizure amelioration effect of omega-3 (n-3) polyunsaturated fatty acids (PUFAs): eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids on patients with DRE from randomized human clinical trials (RCTs).

Methods: The Global Organization for EPA & DHA Omega-3s (GOED) Clinical Study Database was used as the primary search tool to generate a list of RCTs using the following terms: seizures, seizure severity, drug resistant epilepsy, refractory epilepsy, and intractable epilepsy. Subsequently, PubMed and Google Scholar English databases were searched for publications using the additional keywords: eicosapentaenoic acid and docosahexaenoic acid.

Results: Eleven RCTs published before October 2023 were included in this review. EPA and DHA formulations administered to patients ranged between 0.3-2.9g/day, with 90.9% of RCTs investigating the fatty acids at a comparable ratio. A supplementation period of 3 months or less was employed by 72.7% of RCTs. 54.5% of RCTs reported a positive outcome of at least 50% or more significant reduction in seizure frequency compared to placebo or baseline. 27.2% of RCTs reported significant seizure freedom in patients during or at the end of the supplementation period, compared to placebo. Positive outcomes regarding seizure severity remain inconsistent with only 18.1% of RCTs reporting a significant reduction compared to placebo or baseline.

Conclusions: N-3 EPA and DHA have the potential to be a simple add-on treatment intervention for the management of uncontrollable seizures in DRE. Additional RCTs are required to determine the optimal dosage for patients, the effect of long-term

treatment duration and separately enriched preparations of EPA/DHA on seizure frequency and severity.

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PTFS07-03-24 Investigating Specific Molecular and Functional Impacts of Citicoline on Brain Health

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Objectives: Cytidine 5'-diphosphocholine (citicoline) is an endogenously generated nucleotide that serves as an essential intermediate in the synthesis of phosphatidylcholine (PC), the major phospholipid component of human cell membranes. Cognizin®, a citicoline supplement is widely used as a dietary supplement, and supplementation of citicoline has shown beneficial effects on cognitive function and behavior clinically. Despite these encouraging results, the biological mechanisms by which citicoline exerts a neuroprotective effect on brain function and ageing are not completely understood. The objective of this study was to perform an integrative multiomic and predictive modelling analysis to characterize the impacts of citicoline administration on brain health.

Methods: The experiments were performed with a human iPSC-derived tri-culture system consisting of cortical neurons, cortical astrocytes, and microglia cells from BrainXell Inc. Cells were cultivated on MEA plates to have a consistent substrate. The tri-cultures were cultured on 48 well MEAs (Axion Biosystems) for 3-4 weeks until maturation. Maturated cells were treated with citicoline then performed activity recording and RNA Sequencing experiments. The effect of the compounds on the cell activity were assessed using micro-electrode arrays.

Results: Multi-parametric characterization of cell activity after treatment with citicoline or control were recorded. There was a statistically significant dose-dependent response in parameters for cell activity with the treatment of citicoline compared to control. The generation and interrogation of RNA-seq citicoline treatment signatures, accompanied by the investigation of comprehensive network model of neuronal cells revealed the predicted effects of citicoline.

Conclusions: This is the first study to investigate the comprehensive molecular mechanism of citicoline in an in-vitro neuronal tri-culture system with iPSC derived cells. The findings identified the potential impacts and relevance of citicoline supplementation in brain health. However, further analysis is required to decipher the molecular underpinnings of its mechanism of action.

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PTFS07-04-24 Transcriptomic Analyses of Eicosapentaenoic Acid Effects in Adipose Tissue and Cortex From High Fat Diet-Induced Obese Amyloidogenic Alzheimer Disease Mice

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Objectives: Alzheimer's disease (AD) is specified by amyloid-beta (Aβ) plaques and neuroinflammation. Obesity, marked by excessive white adipose tissue (WAT), leads to metabolic dysfunctions, systemic inflammation and enhances risk for AD. We previously reported that eicosapentaenoic acid (EPA), an omega-3 polyunsaturated fatty acids, improved metabolic profiles and reduced serum amyloid β (Aβ40) in diet-induced obese transgenic (TG) amyloidogenic AD mice. Here, we studied the links among obesity, WAT inflammation and neuroinflammation in this AD model.

Methods: To gain mechanistic insights into the metabolic and anti-inflammatory effects of EPA in obese AD mice, male and female APPswePS1E9 TG and non-TG wild-type (WT) littermates were fed HF diets without or with 36g EPA/kg diet (EPA). Metabolic phenotypes were assessed during a 32-week intervention, then blood, WAT (gonadal) and brain (cortex) were collected for further analyses, including fatty acid profiling, and gene expression analyses using RNA-sequencing (RNA Seq) and qRT-PCR. Ingenuity pathway analysis (IPA®) was used to analyze differentially expressed pathways and genes. Data were statistically analyzed by t-test and three-way ANOVA, using GraphPad Prism version 9.

Results: As expected, EPA groups had higher EPA in red blood cells than HF groups ($p < 0.001$). Compared to HF group, EPA reduced NLRP3 gene expression in TG male and female cortex ($p = 0.0205$ and < 0.0001) and in WAT of TG female mice ($p = 0.02$), as assessed by qPCR. RNA Seq analyses using IPA® showed that EPA inhibited oxidative stress ($p < 0.05$) and TNF-a pathways ($p < 0.05$) compared to HF in TG and WT female mice cortex, respectively. Similar analyses in WAT showed that EPA inhibited melatonin degradation 1 ($z = -3.35$, $-\log p = 5.66$) and netrin1($z = -2.82$, $-\log p = 3.84$) pathways in TG males and females, respectively, compared to HF. Moreover, EPA inhibited amyloid fiber formation ($z = -2$, $-\log p = 1.40$) and leukocyte extravasation pathways ($z = -2.64$, $-\log p = 1.56$) in WT males, compared to HF.

Conclusions: EPA protective effects in obese AD mice maybe mediated by inhibition of inflammation/neuroinflammation pathways. Further analyses are required to identify regulatory genes/pathways influencing the links between obesity-induced inflammation and neuroinflammation in AD.

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