

VIRTUAL CONGRESS
of the European Union
Geriatric Medicine Society
(EuGMS)

SYMPOSIUM ABSTRACT BOOK

Satellite Symposium:

**MILD COGNITIVE
IMPAIRMENT: WHEN
NUTRITION HELPS
BRAIN ENERGY RESCUE**

THURSDAY 8th
OCTOBER 2020

SATELLITE SYMPOSIUM

Programme:

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Chairperson: Prof Alfonso Cruz-Jentoft, MD. PhD

Chair of the Geriatric Department. Hospital Universitario Ramón y Cajal (IRYCIS), Madrid, Spain

Past President of the European Geriatric Medicine Society (EuGMS)

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Mild Cognitive Impairment: A silent and late detection disorder

Prof Cornel Sieber, MD. PhD

Chair Internal Medicine- Geriatrics, University Erlangen-Nürnberg. Director Department of Internal Medicine Kantonsspital Winterthur, Switzerland.

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Effect of Ketones on Brain Metabolism: Rationale for Ketotherapeutics

Prof Russell H. Swerdlow, MD. PhD

Director, University of Kansas Alzheimer's Disease Center.

Director, KUMC Neurodegenerative Disorders Program.

University of Kansas School of Medicine.

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Effect of an Oral Nutritional Supplement for improving brain energetics and cognition in Mild Cognitive Impairment

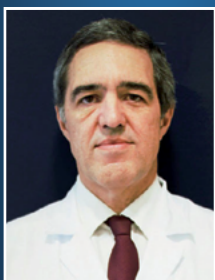
Prof Stephen Cunnane PhD

Research Center on Aging and Department of Medicine. Université de Sherbrooke. Sherbrooke, Québec, Canada

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Q&A with the experts

Chairperson: Prof Alfonso Cruz-Jentoft, MD. PhD



Prof Alfonso J. Cruz-Jentoft,
MD, PhD

Introduction

CHAIRMAN BIOGRAPHY

Prof Alfonso J. Cruz-Jentoft is a physician, specialist in Geriatric Medicine. He currently chairs the Geriatric Department of the Hospital Universitario Ramón y Cajal (IRYCIS), Madrid, Spain. He is professor of Geriatrics at the Universidad Europea de Madrid.

He was President of the European Union Geriatric Medicine Society (EuGMS) and is now member of its Academic Board.

He is Editor-in-Chief of European Geriatric Medicine, the official journal of the EuGMS. Chair of the European Working Group on Sarcopenia in Older People (EWGSOP).

Prof. Cruz-Jentoft is member of the WHO Clinical Consortium on Healthy Ageing. He represents Spain in the Board of the International Association of Gerontology and Geriatrics (IAGG). Serves in the Editorial Board of some major geriatric journals (Age Ageing, J Am Geriatr Soc, JAMDA, JNHA, Aging Clin Exp Res).

ABSTRACT

Mild cognitive impairment (MCI) refers to a transitional stage between normal aging and dementia. MCI is defined by an objective decline in cognitive functioning (using appropriate cognitive tests) that exceeds the expected level given the patient's age and education. Such cognitive changes do not impair social functioning or activities of daily living.

Published prevalence of MCI varies depending on populations and tools used to assess it. The most recent estimates range from 12% to 21% in people aged 60 years or above.

MCI is not always a steady state. It can revert to normal or progress into a dementing disease. Some 35% of people with MCI will eventually progress to Alzheimer's disease or other dementias. The importance of detecting MCI is that it may allow to detect dementia early in the progression of the disease, and thus (potentially) allow to start preventive measures that reduce the rate or at least retard the onset of a clinical dementia.

The World Health Organization (WHO) considers dementia to be a public health priority due to the epidemiological, symptomatic, economic, and humanistic burden of the disease. The seven action areas and targets are shown in this figure.





Their vision of the WHO is “a world in which dementia is prevented and people with dementia and their carers live well and receive the care and support they need to fulfil their potential with dignity, respect, autonomy and equality”. The goal is “to improve the lives of people with dementia, their carers and families, while decreasing the impact of dementia on them as well as on communities and countries”.

Research on MCI is still in progress. Recent guidelines explain that no drugs have proved to be effective for the treatment of MCI. Cholinesterase inhibitors and memantine have frequently been prescribed off-label to patients with MCI despite their lack of efficacy.

Non-pharmacological therapies are a promising alternative to drugs. Physical exercise is effective, at least in the short term. There is still conflicting evidence about cognitive training. Nutritional approaches may have a role: medium-chain triglycerides (MCTs) have been reported to show some beneficial effects.

In this context, the satellite symposium “**Mild Cognitive Impairment: when Nutrition helps Brain Energy Rescue**” intends to enhance the understanding of Mild Cognitive Impairment within geriatric science, to ensure a better understanding of the role that MCT can play to supply energy to brain, and to present the results of innovative Oral Nutritional Supplement containing ketogenic medium chain triglyceride in Mild Cognitive Impairment patients.





Prof. Cornel Sieber,
MD, PhD

Mild Cognitive Impairment: A silent and late detection disorder

SPEAKER BIOGRAPHY

Prof. Cornel Sieber is a physician, specialist in Internal Medicine, Gastroenterology and Hepatology and Geriatric Medicine (University Basle and Hammersmith Hospital London).

At the present time, he is Chair of the Internal Medicine and Geriatric Medicine at the Friedrich-Alexander-Universität Erlangen-Nuremberg, Director Institute for Biomedicine of Aging Nuremberg in Germany. He is Director of the Department of Internal Medicine Kantonsspital Winterthur in Switzerland.

He is President elect at the European Union Geriatric Medicine Society (EuGMS), Vice President Interdisciplinary Center for Gerontology at FAU, and World Health Organization (WHO) member of the "Clinical Consortium on Healthy Ageing" (CCHA).

He was President of the German Society of Internal Medicine (DGIM) (2017-2018), President of the European Academy for Medicine of Ageing (EAMA) (2007-2015), President of the German Society of Nutritional Medicine (DGEM) (2010-2012), and President of the German Society of Geriatrics (DGG) (2005-2008).

He serves on the editorial Boards of different local and international journals. In addition, he is a regular referee to different German and international governmental and private foundations for different fields of Geriatric Medicine.

ABSTRACT

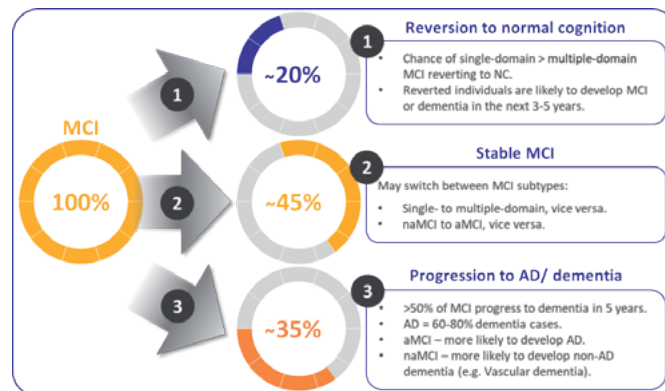
Mild cognitive impairment (MCI) was first described some two decades ago to describe a usual clinical situation: older persons that significantly underperformed in cognitive tests but were functionally able to perform normally. This fact had been described for long and received many names (benign senescent forgetfulness, age associated memory impairment and many other).

Petersen defined MCI as a decline in cognitive functioning that exceeds the expected level given the patient's age and education in one or more cognitive domains, including complex attention, executive functions, language, learning and memory, perceptual-motor domain, and social cognition. Research in MCI increased rapidly, showing that this was an intermediate status between normal cognition and dementia that could potentially open the door to early detection of dementing disorders, so MCI received an ICD-9



code. Persons with MCI may progress to dementia, revert to normal cognition, or remain at MCI. Variants of MCI have been described, the most relevant probably the amnesic subtype (it predicts progression to Alzheimer's disease) and the non-amnesic/multiple deficits subtypes, which predict progression to other dementias, including vascular dementia). Rates of progression are shown in this figure.

Figure: Progression pathway of MCI



AD, Alzheimer's disease; aMCI, amnesic mild cognitive impairment; naMCI, non-amnesic MCI; NC, normal cognition.

Cognitive assessment of MCI is still not fully standardized, with different groups using different tools both in research and clinical settings. MCI remains underdiagnosed, especially among older adults. As MCI is part of the dementia continuum many recommendations for the diagnosis of MCI have been included in dementia clinical practice guidelines. From a geriatric point of view, research is looking to the relations between MCI and the concept of cognitive and physical frailty.

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Prof Russell H. Swerdlow,
MD, PhD

Effect of ketones on brain metabolism: Role of MCTs

SPEAKER BIOGRAPHY

Dr Russell Swerdlow is a professor in the Departments of Neurology, Molecular and Integrative Physiology, and Biochemistry and Molecular Biology at the University of Kansas School of Medicine. He directs the University of Kansas Alzheimer's Disease Center, its Neurodegenerative Disorders Program, and the Heartland Center for Mitochondrial Medicine.

He received undergraduate and MD degrees from New York University, and trained as a neurologist and Alzheimer's specialist at the University of Virginia.

He holds the Gene and Marge Sweeney Chair at the University of Kansas and is a recipient of an S. Weir Mitchell Award from the American Academy of Neurology, a Cotzias Award from the American Parkinson's Disease Association, and a Chancellor's Club Research Award from the University of Kansas.

He currently sits on the National Institute on Aging (NIA) Board of Scientific Counselors. Dr. Swerdlow's research focuses on brain energy metabolism, its role in Alzheimer's disease, and its therapeutic manipulation.

ABSTRACT

Brain energy metabolism declines with advancing age and to a greater extent in certain neurodegenerative diseases of aging. This reflects changes in mitochondrial function, and manifests as well as declining brain glucose utilization. Relevant changes are evident through direct analyses of mitochondria from the brains of aging individuals and those with Alzheimer's disease and its frequent syndromic precursor, mild cognitive impairment. Biomarker tests such as fluorodeoxyglucose positron emission tomography further demonstrate such changes.

Although the underlying basis for these phenomena remains unclear, declining brain energy metabolism may contribute to disease-specific neuropathology and represent a therapeutic target. For these reasons, manipulating brain energy metabolism to treat diseases like Alzheimer's disease mild cognitive impairment are worth exploring. As ketone bodies support brain bioenergetics and ketogenic interventions already feature in the treatment of neurologic disorders, such approaches warrant consideration.

This presentation discusses the rationale, as well as past and recent supporting data, for neuroketotherapeutic interventions in Alzheimer's disease, mild cognitive impairment, and other neurodegenerative diseases. The presentation will especially focus on the rationale for and impact of one



particular neuroketotherapeutic intervention, the ketogenic diet, on the underlying neurodysfunction and cognitive performance of persons with Alzheimer's disease and mild cognitive impairment. Preclinical data from mice placed on a ketogenic diet show a profound impact on molecular pathways implicated in Alzheimer's disease, and indicate the diet may counteract some of those molecular changes. Human pilot studies also report persons with Alzheimer's or mild cognitive impairment showed improved cognitive test scores after initiating a ketogenic diet and achieving ketosis. Despite these encouraging data from preclinical and pilot studies, it is important to keep in mind ketogenic diets affect molecular physiology in multiple ways as they also alter systemic insulin levels and inflammation signaling. Adopting a ketogenic diet also requires a considerable lifestyle commitment, which supports the premise of developing alternative neuroketotherapeutic approaches that may potentially benefit persons with Alzheimer's disease and mild cognitive impairment.

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Prof Stephen
Cunnane, PhD

Effect of an Oral Nutritional Supplement for improving brain energetics and cognition in Mild Cognitive Impairment

SPEAKER BIOGRAPHY

Dr Stephen Cunnane was a professor in the Department of Nutritional Sciences at the University of Toronto for 17 years prior to moving to Sherbrooke, Québec, Canada, in 2003 as a full professor and senior Canada Research Chair at the Research Center on Aging, Université de Sherbrooke. Dr. Cunnane studies whether ketone-based interventions can bypass deteriorating brain glucose metabolism during aging to slow down aging-associated cognitive decline and Alzheimer's disease.

His team was the first to conduct dual tracer PET imaging studies of brain ketone and glucose uptake, and the first to show that the energy status of the Alzheimer brain can improved by ketones. This work led to them showing that a ketogenic supplement can improve cognitive outcomes in the pre-Alzheimer stage - mild cognitive impairment - in direct relation to the increase in brain ketones. Dr. Cunnane has published over 300 research papers and five books. Two of his books highlight the key role of ketones in human brain evolution. His concept of 'brain energy rescue' by ketones to treat neurodegenerative disorders is the subject of his very recent review in Nature Reviews Drug Discovery (to be published in July 2020, Impact Factor of 58).

He was elected to the French National Academy of Medicine in 2009. In 2016, he was honored as a founding Fellow of the International Society for the Study of Fatty Acids and Lipids (ISSFAL). He received the Chevreul Medal from the French Society for the Study of Lipids in 2017 for his research on fats, nutrition and health. In 2018, his team won the Université de Sherbrooke's top research prize for clinical sciences, and he was the Lurie Lecturer at the University of Cincinnati.

Dr. Cunnane consults on the topic of keto-therapeutics and is the founder of Senotec, a start-up company with IP for novel ketogenic molecules.



ABSTRACT

Brain glucose uptake is about 10% below normal in Mild Cognitive Impairment (MCI) and deteriorates further in Alzheimer disease (AD). It is now clear that in contrast to glucose, uptake of the brain's main alternative fuel – ketones (acetoacetate and beta-hydroxybutyrate) – remains normal in both MCI and mild-moderate AD. Furthermore, evidence is accumulating that an endogenous or exogenous source of ketones can at least partially bypass brain glucose hypometabolism and improve brain energy metabolism in both MCI and mild-moderate AD. The key question now is whether improved brain energy metabolism also improves cognitive performance in MCI or AD.

The objective of the randomized, placebo-controlled Benefic trial (NCT02551419) was to assess whether counteracting the brain glucose deficit with an Oral Nutritional Supplement containing a ketogenic medium chain triglyceride (kMCT-ONS), BrainXpert Energy complex, could improve cognitive performance over 6 months in Mild Cognitive Impairment.

Following screening with a comprehensive cognitive battery, n=122 MCI were recruited (amnesic and non-amnesic MCI combined). An overall sample size of n=82 for both arms combined was required to have the necessary power to detect at least a moderate effect size on cognitive outcomes of episodic memory and executive function. Outcomes in all five main cognitive domains were assessed immediately before and at the end of the intervention.

The ONS was lactose-free skim milk emulsion containing 15 g kMCT twice/day (active arm; n=39 completers) or an energy equivalent placebo providing 12 g non-ketogenic vegetable oil twice/day (n=44 completers). The formulation and organoleptic properties of the ONS were identical for both active and placebo arms.

Brain ketone and glucose PET were done before and at the end of the 6-month intervention on sub-groups of both arms (n=19/arm pre- and post-intervention). The plasma ketone response was assessed before and after the intervention in a different sub-group (n=10/arm pre- and post-intervention). Plasma cardiometabolic and inflammatory marker profiles were also assessed.

Data were analyzed by ANCOVA using pre-intervention cognitive score plus age, sex, education and apolipoprotein E4 status combined as covariates.

Raw scores as well as normalized Z-scores for five tests in three cognitive domains improved post-intervention on the kMCT arm only ($p \leq 0.01$). Specifically, on the kMCT-ONS, trial 1 of the:

- Free and Cued Recall Test showed a +1 word improvement (+0.5 Δ Z-score),
- Correct answers on the Verbal Fluency Test increased by 2 words (+0.3 Δ Z-score) but decreased by 1 word on placebo (-0.1 Δ Z-score),
- Correct answers on the Boston Naming Test increased by 1.1,



- Time taken on the Stroop Colour Naming Test decreased by 1 sec ($p=0.09$),
- Errors on the Trail Making Test decreased by 0.9 on the kmct-ONS but increased by 0.8 on placebo ($p=0.02$).

Global brain ketone uptake doubled on the kmCT-ONS only and directly as the increase in plasma ketones ($r = +0.87$, $p<0.01$). Moderate effect sizes (partial $\eta^2 = 0.06 - 0.14$) were seen for several cognitive outcomes on the kmCT-ONS only.

Free and cued recall, Trail-making, and Boston Naming test scores all correlated significantly and directly as the increase in plasma or global brain ketone uptake on kmCT-ONS ($r = +0.23 - +0.33$, $p = 0.013 - 0.042$). Increased uptake of ketones in multiple brain white matter fascicles was significantly positively correlated with faster processing speed on the kmCT-ONS ($r = +0.47 - +0.61$, $p = 0.014 - 0.047$; $n=16$). Plasma ketone response to a single 15-gram dose of the kmCT-ONS did not change significantly at the end vs. before the 6-month intervention; ketones did not increase at all on the placebo arm. Changes in anthropometry (weight, BMI) and plasma markers of cardiometabolic health (insulin, glucose, cholesterol) were not clinically significant post-intervention on either arm. Amongst the plasma inflammatory markers, only interleukin 8 increased on the kmCT-ONS (+3 pg/ml; interaction $p = 0.002$ vs. post-placebo; $n=17$). Average drop-out rate on both arms was 31%. In completers, protocol adherence was 89% over six months.

Conclusions:

The Benefic Trial was powered to assess outcomes of memory and executive function in Mild Cognitive Impairment and demonstrated that this Oral Nutritional Supplement containing a ketogenic medium chain triglyceride (kmCT-ONS), BrainXpert Energy complex, improved several cognitive outcomes that were positively correlated with the improved brain energy status achieved by the enhanced supply of ketones.

Hence, there was a direct mechanistic link between raising brain ketones with the kmCT-ONS and improving cognitive performance in MCI. The consistent plasma ketone response suggests there was no metabolic adaptation or loss of response to an oral dose of kmCT-ONS after daily consumption over six months.

These results demonstrate efficacy, safety, acceptability, and feasibility of long-term use of BrainXpert Energy complex twice daily dose to improve cognitive performance in MCI.

Disclosures: Financial support for the Benefic Trial was provided by the Alzheimer Association USA, FRQS, Université de Sherbrooke and Nestlé Health Science. Abitec provided the kmCT (Captex 355) and placebo oil (high oleic acid sunflower oil). The ONS for both arms was prepared under contract at INAF, Université Laval, Québec, QC, Canada. SCC has consulted for or received travel honoraria or test products for research from Nestlé Health Science, Bulletproof, Cerecin, and Abitec. SCC is the founder and director of the consulting company, Senotec Ltd.



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