Sökning i databaser för vetenskaplig evidens: Souvenaid® kosttillskott vid tidig Alzheimers sjukdom

Frågeställning

Vilken dagsaktuell vetenskaplig evidens finns för att kosttillskottet Souvenaid® är en effektiv och kostnadseffektiv behandling vid tidig Alzheimers sjukdom

Bakgrund

Kosttillskott har sedan decennier föreslagits som värdefull behandling eller komplement till annan behandling vid olika sjukdomstillstånd. Solid vetenskaplig evidens för betydelsefulla effekter utöver den som optimal kosthållning ger saknas oftast (Espin, Garcia-Conesa et al. 2007).

Alzheimers sjukdom är en neurodegerativ sjukdom som karakteriseras av inlagringar i hjärnan och successivt bristande hjärnfunktioner. Initialt främst bristande minnesfunktioner. Hypotesen bakom användning av kosttillskott vid Alzheimers sjukdom är att brist på näringsämnen viktiga för hjärnfunktionen kan påverka minne och andra hjärnfunktioner, som skulle kunna förbättras med tillskott (Weiner 1990; Wurtman 2008; Wurtman, Cansev et al. 2009) av t ex uridin, kolin, fosfolipider, fleromättade fettsyror, selen och vitaminerna E, C, B_{12} och B_6 som är viktiga ingredienser i Souvenaid®. Rekommenderat kosttillskott med Souvenaid® kostar ca 10 000 SKR pr. patient pr. år.

Metodrådets sammanfattande bedömning

Befintliga vetenskapliga studier visar inga (Shah, Kamphuis et al. 2013) eller enbart måttliga effekter (Scheltens, Twisk et al. 2012) på symptomen vid Alzheimers sjukdom, och då enbart i sjukdomens tidigaste stadier. Intag av Souvenaid® bromsar inte sjukdomsutvecklingen, men tolereras väl och påverkar inte konventionell läkemedelsbehandling. Vetenskapliga studier pågår av Souvenaid® vid olika stadier av Alzheimers sjukdom på båda sidor av Atlanten.

Det finns i dagsläget inte vetenskaplig evidens för att kosttillskottet Souvenaid® är en effektiv behandling vid tidig Alzheimers sjukdom.

Sökning i HTA (Health Technology Assessment) databaser (2013-12-15)

*SBU - Kunskapscentrum för hälso- och sjukvård*en http://www.sbu.se/sv/

Inga träffar på ”Souvenaid”

Socialstyrelsen – nationella riktlinjer
http://www.socialstyrelsen.se/riktlinjer/nationellariktlinjer

Inga träffar på ”Souvenaid”

TRIP databasen http://www.tripdatabase.com/search/advanced

9 träffar på ”Souvenaid”. Samtliga refereras till på andra ställen i denna rapport, utom den sammanfattning som refereras till nedan.

År 2014: “Souvenaid is a dietary supplement marketed as a medicinal food for the treatment of early Alzheimer’s disease (AD). It is purported to improve cognitive performance by supporting synapse formation and function. Three randomised controlled trails failed to show a significant effect of Souvenaid in decreasing the rate of cognitive decline or delaying AD progression. There may be a small effect on memory performance in drug-naïve persons in the very early stages of disease." (Australia 2014)

*The Cochrane Lib*rary http://www.thecochranelibrary.com/view/0/index.html

Sju träffar på ”Souvenaid”

Samtliga refererar till studier som upptas i detta dokument eller till register över motsvarande kliniska prövningar

Clinical Evidence http://www.clinicalevidence.com/x/index.html

Inga träffar på ”Souvenaid”

International Network of Agencies for Health Technology Assessment http://www.inahta.net/

Inga träffar på ”Souvenaid”

Nasjonalt kunnskapssenter for helsetjenesten, Norge http://www.kunnskapssenteret.no/

Ingen träff på ”Souvenaid”.

Annan vetenskaplig evidens

Åtminstone tre randomiserade och kontrollerade studier av effekten av Souvenaid® på tidig Alzheimers sjukdom föreligger (Scheltens, Kamphuis et al. 2010; Kamphuis, Verhey et al. 2011; Carrasco-Gallardo, Farias et al. 2012; Scheltens, Twisk et al. 2012; Shah, Kamphuis et al. 2013; de Waal, Stam et al. 2014). **Souvenir II- studien** från 2012 inkluderade 266 randomiserade patienter (Cummings 2012; Scheltens, Twisk et al. 2012; de Waal, Stam et al. 2014). Effekten på minnesfunktioner efter 24 månaders behandling var 0,21 sk Coehn´s d som betyder att patienterna behandlade med Souvenaid hade minnesfunktioner som var 21 % av en standardavvikelse bättre efter 24 veckors behandling. I **S-Connect dubbelblinda multicenter studien** visade å andra sidan Shah och medarbetare år 2013 (Shah, Kamphuis et al. 2013) ingen skillnad mellan kontroll- och behandlad grupp efter 24 veckor. Studien inkluderade 527 patienter som behandlades med traditionell Alzheimers medicinering och

tillägg av Souvenaid® eller föda med identiskt kaloriinnehåll. Souvenaid® minskade inte heller progressen av Alzheimers sjukdom hos de behandlade patienterna.

Ingen av de publicerade studierna av Souvenaid® har inkluderat en kontrollgrupp där patienterna fått rådgivning om optimal vanlig kost.

Etisk bedömning

Souvenaid® marknadsförs och säljs som kosttillskott. De som drabbats av Alzheimer och deras närstående kan komma att vilja använda detta kosttillskott i brist på andra biverkningsfria behandlingsalternativ trots årlig kostnad på ca 10 000 SKR/ patient och bristande vetenskaplig evidens.

Metodrådet i Sydöstra sjukvårdsregionen den 26 februari 2014
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Litteraturreferenser

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Carrasco-Gallardo, C., G. A. Farias, et al. (2012). "Can Nutraceuticals Prevent Alzheimer's Disease? Potential Therapeutic Role of a Formulation Containing Shilajit and Complex B Vitamins." Archives of Medical Research **43**(8): 699-704.

Alzheimer's disease (AD) is a brain disorder displaying a prevalence and impact in constant expansion. This expansive and epidemic behavior is concerning medical and public opinion while focusing efforts on its prevention and treatment. One important strategy to prevent this brain impairment is based on dietary changes and nutritional supplements, functional foods and nutraceuticals. In this review we discuss the potential contributions of shilajit and complex B vitamins to AD prevention. We analyze the status of biological studies and present data of a clinical trial developed in patients with mild AD. Studies suggest that shilajit and its active principle fulvic acid, as well as a formula of shilajit with B complex vitamins, emerge as novel nutraceutical with potential uses against this brain disorder. (c) 2012 IMSS. Published by Elsevier Inc.

Cummings, J. L. (2012). "Food for thought: Souvenaid in mild Alzheimer's disease." J Alzheimers Dis **31**(1): 237-238.

de Waal, H., C. J. Stam, et al. (2014). "The effect of souvenaid on functional brain network organisation in patients with mild Alzheimer's disease: a randomised controlled study." PLoS One **9**(1): e86558.

BACKGROUND: Synaptic loss is a major hallmark of Alzheimer's disease (AD). Disturbed organisation of large-scale functional brain networks in AD might reflect synaptic loss and disrupted neuronal communication. The medical food Souvenaid, containing the specific nutrient combination Fortasyn Connect, is designed to enhance synapse formation and function and has been shown to improve memory performance in patients with mild AD in two randomised controlled trials. OBJECTIVE: To explore the effect of Souvenaid compared to control product on brain activity-based networks, as a derivative of underlying synaptic function, in patients with mild AD. DESIGN: A 24-week randomised, controlled, double-blind, parallel-group, multi-country study. PARTICIPANTS: 179 drug-naive mild AD patients who participated in the Souvenir II study. INTERVENTION: Patients were randomised 1ratio1 to receive Souvenaid or an iso-caloric control product once daily for 24 weeks. OUTCOME: In a secondary analysis of the Souvenir II study, electroencephalography (EEG) brain networks were constructed and graph theory was used to quantify complex brain structure. Local brain network connectivity (normalised clustering coefficient gamma) and global network integration (normalised characteristic path length lambda) were compared between study groups, and related to memory performance. RESULTS:

THE NETWORK MEASURES IN THE BETA BAND WERE SIGNIFICANTLY DIFFERENT BETWEEN GROUPS: they decreased in the control group, but remained relatively unchanged in the active group. No consistent relationship was found between these network measures and memory performance. CONCLUSIONS: The current results suggest that Souvenaid preserves the organisation of brain networks in patients with mild AD within 24 weeks, hypothetically counteracting the progressive network disruption over time in AD. The results strengthen the hypothesis that Souvenaid affects synaptic integrity and function. Secondly, we conclude that advanced EEG analysis, using the mathematical framework of graph theory, is useful and feasible for assessing the effects of interventions. TRIAL REGISTRATION: Dutch Trial Register NTR1975.

Espin, J. C., M. T. Garcia-Conesa, et al. (2007). "Nutraceuticals: facts and fiction." Phytochemistry **68**(22-24): 2986-3008.

Epidemiological studies show a link between the consumption of plant-derived foods and a range of health benefits. These benefits have been associated, at least partially, to some of the phytochemical constituents, and, in particular, to polyphenols. In the last few years, nutraceuticals have appeared in the market. These are pharmaceutical forms (pills, powders, capsules, vials, etc.) containing food bioactive compounds as active principles. The bioactive phytochemicals have become a very significant source for nutraceutical ingredients. Scientific research supports the biological activity of many of these food phytochemicals, but the health claims attributed to the final marketed nutraceutical products have often little or doubtful scientific foundation. This is due to the fact that a lot of the scientific evidence is derived from animal testing and in vitro assays, whereas human clinical trials are scarce and inconclusive. Some key issues such as bioavailability, metabolism, dose/response and toxicity of these food bioactive compounds or the nutraceuticals themselves have not been well established yet. Amongst the phytochemicals, several groups of polyphenols (anthocyanins, proanthocyanidins, flavanones, isoflavones, resveratrol and ellagic acid) are currently used in the nutraceutical industry. In this report, we have reviewed the most recent scientific knowledge on the bioavailability and biological activity of these polyphenols ('fact'), as well as the health claims (which are not always supported by scientific studies) ascribed to the polyphenols-containing nutraceuticals ('fiction'). The in vitro antioxidant capacity, often used as a claim, can be irrelevant in terms of in vivo antioxidant effects. Bioavailability, metabolism, and tissue distribution of these polyphenols in humans are key factors that need to be clearly established in association to the biological effects of these polyphenols-containing nutraceuticals. The future trends of phytochemistry research regarding nutraceuticals are discussed.

Kamphuis, P. J., F. R. Verhey, et al. (2011). "Effect of a medical food on body mass index and activities of daily living in patients with Alzheimer's disease: secondary analyses from a randomized, controlled trial." J Nutr Health Aging **15**(8): 672-676.

OBJECTIVES: To investigate the effect of a medical food (Souvenaid) on body mass index (BMI) and functional abilities in patients with mild Alzheimer's disease (AD).

DESIGN/SETTING/PARTICIPANTS/INTERVENTION /MEASUREMENTS: These analyses were performed on data from a 12-week, double-blind, randomized, controlled, multicenter, proof-of-concept study with a similarly designed and exploratory 12-week extension period. Patients with mild AD (Mini-Mental State Examination score of 20-26) were randomized to receive either the active product or an iso-caloric control product. While primary outcomes included measures of cognition, the 23-item Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scale was included as a secondary outcome. Both ADCS-ADL and BMI were assessed at baseline and Weeks 6, 12 and 24. Data were analyzed using a repeated-measures mixed model. RESULTS: Overall, data suggested an increased BMI in the active versus the control group at Week 24 (ITT: p = 0.07; PP: p = 0.03), but no treatment effect on ADCS-ADL was observed. However, baseline BMI was found to be a significant treatment effect modifier (ITT: p = 0.04; PP: p = 0.05), and an increase in ADCS-ADL was observed at Week 12 in patients with a 'low' baseline BMI (ITT: p = 0.02; PP: p = 0.04). CONCLUSIONS: These data indicate that baseline BMI significantly impacts the effect of Souvenaid on functional abilities. In addition, there was a suggestion that Souvenaid increased BMI.

Scheltens, P., P. J. Kamphuis, et al. (2010). "Efficacy of a medical food in mild Alzheimer's disease: A randomized, controlled trial." Alzheimers Dement **6**(1): 1-10 e11.

OBJECTIVE: To investigate the effect of a medical food on cognitive function in people with mild Alzheimer's disease (AD). METHODS: A total of 225 drug-naive AD patients participated in this randomized, double-blind controlled trial. Patients were randomized to active product, Souvenaid, or a control drink, taken once-daily for 12 weeks. Primary outcome measures were the delayed verbal recall task of the Wechsler Memory Scale-revised, and the 13-item modified Alzheimer's Disease Assessment Scale-cognitive subscale at week 12. RESULTS: At 12 weeks, significant improvement in the delayed verbal recall task was noted in the active group compared with control (P = .021). Modified Alzheimer's Disease Assessment Scale-cognitive subscale and other outcome scores (e.g., Clinician Interview Based Impression of Change plus Caregiver Input, 12-item Neuropsychiatric Inventory, Alzheimer's disease Co-operative Study-Activities of Daily Living, Quality of Life in Alzheimer's Disease) were unchanged. The control group neither deteriorated nor improved. Compliance was excellent (95%) and the product was well tolerated. CONCLUSIONS: Supplementation with a medical food including phosphatide precursors and cofactors for 12 weeks improved memory (delayed verbal recall) in mild AD patients. This proof-of-concept study justifies further clinical trials.

Scheltens, P., J. W. Twisk, et al. (2012). "Efficacy of Souvenaid in mild Alzheimer's disease: results from a randomized, controlled trial." J Alzheimers Dis **31**(1): 225-236.

Souvenaid aims to improve synapse formation and function. An earlier study in patients with Alzheimer's disease (AD) showed that Souvenaid increased memory performance after 12 weeks in drug-naive patients with mild AD. The Souvenir II study was a 24-week, randomized, controlled, double-blind, parallel-group, multi-

country trial to confirm and extend previous findings in drug-naive patients with mild AD. Patients were randomized 1:1 to receive Souvenaid or an iso-caloric control product once daily for 24 weeks. The primary outcome was the memory function domain Z-score of the Neuropsychological Test Battery (NTB) over 24 weeks. Electroencephalography (EEG) measures served as secondary outcomes as marker for synaptic connectivity. Assessments were done at baseline, 12, and 24 weeks. The NTB memory domain Z-score was significantly increased in the active versus the control group over the 24-week intervention period ($p = 0.023$; Cohen's $d = 0.21$; 95% confidence interval [-0.06]-[0.49]). A trend for an effect was observed on the NTB total composite z-score ($p = 0.053$). EEG measures of functional connectivity in the delta band were significantly different between study groups during 24 weeks in favor of the active group. Compliance was very high (96.6% [control] and 97.1% [active]). No difference between study groups in the occurrence of (serious) adverse events. This study demonstrates that Souvenaid is well tolerated and improves memory performance in drug-naive patients with mild AD. EEG outcomes suggest that

Souvenaid has an effect on brain functional connectivity, supporting the underlying hypothesis of changed synaptic activity.

Shah, R. C., P. J. Kamphuis, et al. (2013). "The S-Connect study: results from a randomized, controlled trial of Souvenaid in mild-to-moderate Alzheimer's disease." Alzheimers Res Ther **5**(6): 59.

INTRODUCTION: Souvenaid(R) containing Fortasyn(R) Connect is a medical food designed to support synapse synthesis in persons with Alzheimer's disease (AD). Fortasyn Connect includes precursors (uridine monophosphate; choline; phospholipids; eicosapentaenoic acid; docosahexaenoic acid) and cofactors (vitamins E, C, B12, and B6; folic acid; selenium) for the formation of neuronal membranes. Whether Souvenaid slows cognitive decline in treated persons with mild-to-moderate AD has not been addressed. METHODS: In a 24-week, double-masked clinical trial at 48 clinical centers, 527 participants taking AD medications [52% women, mean age 76.7 years (Standard Deviation, SD = 8.2), and mean Mini-Mental State Examination score 19.5 (SD = 3.1, range 14-24)] were randomized 1:1 to daily, 125-mL (125 kcal), oral intake of the active product (Souvenaid) or an iso-caloric control. The primary outcome of cognition was assessed by the 11-item Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog). Compliance was calculated from daily diary recordings of product intake. Statistical analyses were performed using mixed models for repeated measures. RESULTS: Cognitive performance as assessed by ADAS-cog showed decline over time in both control and active study groups, with no significant difference between study groups (difference =0.37 points, Standard Error, SE = 0.57, p = 0.513). No group differences in adverse event rates were found and no clinically relevant differences in blood safety parameters were noted. Overall compliance was high (94.1% [active] and 94.5% [control]), which was confirmed by significant changes in blood (nutritional) biomarkers. CONCLUSIONS: Add-on intake of Souvenaid during 24 weeks did not slow cognitive decline in persons treated for mild-to-moderate AD. Souvenaid was well tolerated in combination with standard care AD medications. TRIAL REGISTRATION: Dutch Trial Register number: NTR1683.

Weiner, M. (1990). "Suspected Dietary Factors in Alzheimers-Disease." Neurobiology of Aging **11**(3): 295-295.

Wurtman, R. J. (2008). "Synapse formation and cognitive brain development: effect of docosahexaenoic acid and other dietary constituents." Metabolism **57 Suppl 2**: S6-10.

The brain is unusual among organs in that the rates of many of its characteristic enzymatic reactions are controlled by the local concentrations of their substrates, which also happen to be nutrients that cross the blood-brain barrier. Thus, for example, brain levels of tryptophan, tyrosine, or choline can control the rates at which neurons synthesize serotonin, dopamine, or acetylcholine, respectively. The rates at which brain cells produce membrane phospholipids such as phosphatidylcholine (PC) are also under such control, both in adult animals and, especially, during early

development. If pregnant rats are fed the 3 dietary constituents needed for PC synthesis- docosahexaenoic acid, uridine, and choline-starting 10 days before parturition and continuing for 20 days during nursing, brain levels of PC, and of the other membrane phosphatides (per cell or per mg protein), are increased by 50% or more. In adult animals, this treatment is also known to increase synaptic proteins (eg, synapsin-l, syntaxin-3, GluR-l, PSD-95) but not ubiquitous proteins like beta-tubulin and to increase (by 30% or more) the number of dendritic spines on hippocampal neurons. Docosahexaenoic acid currently is widely used, in human infants, to diminish the negative effects of prematurity on cognitive development. Moreover, docosahexaenoic acid, uridine (as uridine monophosphate), and choline are all found in mother's milk, and included in most infant formulas. It is proposed that these substances are part of a regulatory mechanism through which plasma composition influences brain development.

Wurtman, R. J., M. Cansev, et al. (2009). "Synapse formation is enhanced by oral administration of uridine and DHA, the circulating precursors of brain phosphatides." J Nutr Health Aging **13**(3): 189-197.

OBJECTIVE: The loss of cortical and hippocampal synapses is a universal hallmark of Alzheimer's disease, and probably underlies its effects on cognition. Synapses are formed from the interaction of neurites projecting from "presynaptic" neurons with dendritic spines projecting from "postsynaptic" neurons. Both of these structures are vulnerable to the toxic effects of nearby amyloid plaques, and their loss contributes to the decreased number of synapses that characterize the disease. A treatment that increased the formation of neurites and dendritic spines might reverse this loss, thereby increasing the number of synapses and slowing the decline in cognition. DESIGN SETTING, PARTICIPANTS, INTERVENTION, MEASUREMENTS AND RESULTS: We observe that giving normal rodents uridine and the omega-3 fatty acid docosahexaenoic acid (DHA) orally can enhance dendritic spine levels (3), and cognitive functions (32). Moreover this treatment also increases levels of biochemical markers for neurites (i.e., neurofilament-M and neurofilament-70) (2) in vivo, and uridine alone increases both these markers and the outgrowth of visible neurites by cultured PC-12 cells (9). A phase 2 clinical trial, performed in Europe, is described briefly. DISCUSSION AND CONCLUSION: Uridine and DHA are circulating precursors for the phosphatides in synaptic membranes, and act in part by increasing the substrate-saturation of enzymes that synthesize phosphatidylcholine from CTP (formed from the uridine, via UTP) and from diacylglycerol species that contain DHA: the enzymes have poor affinities for these substrates, and thus are unsaturated with them, and only partially active, under basal conditions. The enhancement by uridine of neurite outgrowth is also mediated in part by UTP serving as a ligand for neuronal P2Y receptors. Moreover administration of uridine with DHA activates many brain genes, among them the gene for the m-1 metabotropic glutamate receptor [Cansev, et al, submitted]. This activation, in turn, increases brain levels of that gene's protein product and of such other synaptic proteins as PSD-95, synapsin-1, syntaxin-3 and F-actin, but not levels of non-synaptic brain proteins like beta-tubulin. Hence it is possible that giving uridine plus DHA triggers a neuronal program that, by

accelerating phosphatide and synaptic protein synthesis, controls synaptogenesis. If administering this mix of phosphatide precursors also increases synaptic elements in brains of patients with Alzheimer 's disease, as it does in normal rodents, then this treatment may ameliorate some of the manifestations of the disease.