LEADING ARTICLE

Drugs Aging 2011; 28 (6): 421-428
1170-229X/11/0006-0421/$49.95/0

Medical Foods for Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a neurodegenerative condition associated with cognitive loss, behavioural changes, functional ability decline and caregiver burden. Given the worldwide public health impact of AD, novel interventions to reduce suffering experienced by AD patients need to be developed. Foods may offer a mechanism for intervention complementary to drugs, devices, biologicals and vaccines. Apart from foods with health claims (including dietary supplements), medical foods are also being explored as an intervention option. The purpose of this article is to describe how medical foods may complement other interventions for AD patients by: (i) defining what a medical food is; (ii) discussing whether AD is a condition amenable to medical food intervention; (iii) reviewing current clinical trial data on medical foods used in participants with AD; and (iv) highlighting steps needed to establish a more comprehensive framework for developing medical foods for AD. While medical foods may be defined differently in other countries, the US Orphan Drug Act of 1998 defined a medical food as a food formulated for enteral intake, taken under physician supervision, and intended to meet the distinctive nutritional requirements identified for a disease or condition. For AD to be amenable to medical food intervention, it must: (i) result in limited or impaired capacity to ingest, digest, absorb or metabolize ordinary foodstuff or certain nutrients; or (ii) have unique, medically determined nutrient requirements; and (iii) require dietary management that cannot be achieved by modification of the normal diet alone. While these criteria are most likely met in advanced AD, identifying unique nutritional requirements in early AD that cannot be met by normal diet modification requires a better understanding of AD pathophysiology. A PubMed search using the terms 'medical food' and 'Alzheimer', limited to clinical trials published in English with human participants with AD aged >65 years and supplemented by other articles known to meet the inclusion criteria, revealed that only two medical foods, AC-1202 and Souvenaid® with Fortasyn Connect™, have clinical trial results available for discussion. As medical food development for AD is a relatively new endeavour, a window of opportunity exists for all stakeholders to develop a comprehensive framework for assuring that medical food interventions for AD achieve the highest possible scientific and ethical standards to warrant commercialization.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative condition associated with cognitive loss, behavioural changes, functional ability decline and caregiver burden. The global number of persons living with AD is estimated to increase from 35.6 million in 2010 to 115.4 million by 2050.[1] In 2010, AD resulted in global indirect and direct care costs estimated at $US604 billion annually, with about 70% of the global costs occurring in Western Europe and North America.[2] Given the worldwide public health impact of AD, continued efforts are needed to simultaneously develop novel AD interventions and AD preventative measures.

The development of novel AD interventions has tended to parallel new treatments in other conditions with large public health impacts (cardiovascular disease, cancer and depression) and new hypotheses regarding AD pathogenesis. The initial focus on developing small molecule compounds to alter brain neurotransmitter levels led to the approval by the US FDA of five drugs for the symptomatic treatment of AD (tacrine, donepezil, galantamine, rivastigmine and memantine).[3-5] Limited interventions using devices for AD have been under development.[6] With advances in recombinant therapies and monoclonal antibodies, efforts in various phases of clinical development have focused on immunotherapy targeting β-amyloid protein synthesis, accumulation and elimination,[7] in addition to biologicals such as recombinant growth factors.[8] While many dietary supplements are commercially available, only a few have been tested in clinical trials with AD patients.[9] As an entity between foods with health claims (including dietary supplements) and drugs, medical foods have generated recent interest, especially with the 2009 commercial introduction in the US of a medical food to meet a potential nutritional need of AD patients.[10]

Stakeholders interested in reducing the suffering associated with AD have limited exposure to the concept of medical foods. Therefore, the purpose of this article is to describe the role medical foods may play as novel interventions for AD patients. First, it is important to provide a definition of medical foods and to understand how medical foods differ from other therapeutic options. Second, whether AD is a disease amenable to medical food intervention requires discussion. Third, a review of current clinical trial results of medical food interventions in persons diagnosed with AD is provided. Finally, issues that need to be resolved in the future to clarify the role of medical foods in AD are highlighted.

2. Definition of a Medical Food

The boundaries between medical foods and other foods with health claims or drugs are based on legal definitions, health claim abilities and regulatory oversight. The boundaries are subject to interpretation and are not always easily understood by researchers, clinicians or consumers. In certain situations, a particular biochemical entity may qualify for some or all categories. For instance, the practice of enhancing omega-3 fatty acid intake by eating fish to maintain membrane function of healthy brain cells could enable fish to be classified as a conventional food with a health claim. If the omega-3 is concentrated from fish oil, encapsulated and ingested to maintain membrane function of healthy brain cells, then omega-3 could be a dietary supplement. If omega-3 is processed from algae membranes to meet the specific nutritional needs of a person with AD who loses synapses due to omega-3 fatty acid deficiencies that cannot be made up solely by eating more fish, then omega-3 can be classified as a medical food. Finally, if omega-3 is described as a treatment for slowing cognitive decline in AD, then omega-3 can be classified as a drug.

In the US, food types include conventional foods, dietary supplements and medical foods. Conventional foods are foods not designated as dietary supplements and are labelled with 'Nutrition Facts'.[11] As defined by the US Congress in the Dietary Supplement Health and Education Act of 1994 (DSHEA), dietary supplements are products containing a vitamin or mineral, a herb or other botanical, an amino acid or a dietary substance for human use to supplement the diet by increasing the total dietary intake; a concentrate, metabolite or extract; or a combination

Table I. US FDA criteria for a medical food (reproduced from FDA[15])

A food is a medical food exempt from nutrition labelling only if:
a. It is a specially formulated and processed product (as opposed to a naturally occurring foodstuff used in its natural state) for the partial or exclusive feeding of a patient by means of oral intake or enteral feeding by tube
b. It is intended for the dietary management of a patient who, because of therapeutic or chronic medical needs, has limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients, or who has other special medically determined nutrient requirements, the dietary management of which cannot be achieved by the modification of the normal diet alone
c. It provides nutritional support specifically modified for the management of the unique nutrient needs that result from the specific disease or condition, as determined by medical evaluation
d. It is intended to be used under medical supervision; and it is intended only for a patient receiving active and ongoing medical supervision wherein the patient requires medical care on a recurring basis for, among other things, instructions on the use of the medical food

of the preceding ingredients.[12] Dietary supplements are labelled with 'Supplement Facts'. Dietary supplements and conventional foods can make health claims that describe their effect on normal structure or function in humans.[13] In section 5(b) of the 1998 Orphan Drug Act [21 US Code 360ee (b) (3)], a medical food is defined as a food "formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."[14] Criteria clarifying the statutory definition of medical foods [21 Code of Federal Regulations 101.9 (j) (8)] are provided in table I.[15] A medical food can be labelled as meeting the nutritional needs for a particular disease or condition.

There are several key features that determine if a food can be deemed a medical food rather than a conventional food or dietary supplement (table II). A medical food must be formulated with ingredients approved as food additives or ingredients subject to exemption for investigational use, if not on the Generally Recognized as Safe (GRAS) list.[15] A medical food requires ongoing medical supervision and instruction, while other food categories do not.

In contrast to drugs, medical foods must be administered enterally, can be the sole source of nutritional needs, and must be formulated. A drug can make a claim to "diagnose, treat, cure or prevent any disease"[11] in a package insert while a medical food cannot make such health claims. In the US, medical foods are under the regulatory purview of the Center for Food Safety and Applied Nutrition (CFSAN) rather than the Center for Drug Evaluation and Research

Table II. Characteristics of medical foods versus other types of foods or drugs in the US

Characteristic	Intervention type			
	food			drug
	conventional food	dietary supplement	medical food	
Enteral intake only	Yes	Yes	Yes	No
Can be sole source of nutritional needs	Yes	No	Yes	No
Must be formulated	No	No	Yes	No
Requires medical supervision	No	No	Yes	Yes
US FDA approval needed before marketing	No	No	No	Yes
Allowable health claim	Effect on normal structure/function	Effect on normal structure/function	Nutritional needs for disease or condition	Diagnosis, treatment, or prevention of disease or condition
Health claim labelling	Nutrition Facts	Supplement Facts	Nutrition Facts	Package insert
FDA regulatory centre	CFSAN	CFSAN	CFSAN	CDER

CDER = Center for Drug Evaluation and Research; **CFSAN** = Center for Food Safety and Applied Nutrition.

(CDER) at the FDA. While CDER reviews specific pre-clinical and clinical safety and efficacy data collected in order to approve a New Drug Application, CFSAN does not have a legislative mandate to ensure medical foods undergo a similar pre-market review or approval process.[15] Instead, CFSAN oversees a medical food compliance programme.[15]

Products considered medical foods in the US would most likely be regulated under dietary foods for special medical purposes in the EU. Dietary foods for special medical purposes are ''for particular nutritional uses specially processed or formulated and intended for the dietary management of patients and to be used under medical supervision. They are intended for the exclusive or partial feeding of patients with a limited, impaired or disturbed capacity to take, digest, absorb, metabolise or excrete ordinary foodstuffs or certain nutrients contained therein or metabolites, or with other medically-determined nutrient requirements, whose dietary management cannot be achieved only by modification of the normal diet, by other foods for particular nutritional uses, or by a combination of the two.''[16] The EU also provides a detailed list of approved ingredients for use in foods for special medical purposes.[17]

3. Alzheimer's Disease as a Condition Amenable to Medical Food Intervention

In order to be considered a disease amenable to medical food intervention, AD must: (i) result in limited or impaired capacity to ingest, digest, absorb or metabolize ordinary foodstuffs or certain nutrients; or (ii) have unique, medically determined nutrient requirements; and (iii) require dietary management that cannot be achieved by modification of the normal diet alone.

AD meets the first criterion, as individuals with the disease do develop limited or impaired capacity to ingest ordinary foodstuffs. During the natural course of AD, individuals lose the ability to shop for groceries and prepare meals in the mild-to-moderate stage, lose the ability to feed themselves in the moderate-to-severe stage, and forget how to chew and swallow food in the advanced stage. While individuals with advanced AD have macronutrient requirements that cannot be obtained by modification of the normal diet alone, the use of enteral formula feeds has not been shown to have benefits that outweigh the risks.[18] Whether less advanced AD is associated with unique macronutrient needs that surpass normal diet modifications is not clear. Individuals with AD are more likely to have macronutrient needs as they tend to lose body mass index.[19,20] The macronutrient needs may result from having less access to food sources due to changes in acquiring food, preparing food and self-capability to ingest food associated with AD. Access barriers may be overcome by having a caregiver available to assist with food gathering and preparation tasks or by modifying food consistency to make ingestion easier.[21,22] However, research points to alterations in food preferences, chronic inflammatory processes, and changes in energy metabolism occurring with AD.[19,23,24] These metabolic changes may result in unique nutrient needs that cannot be overcome by simple modification of a normal diet.

Apart from macronutrient needs, AD may result in certain unique micronutrient needs at various disease stages. The manifestation of AD symptoms is associated with loss of neuronal function. Deficits due to impaired capacity to ingest and metabolize certain nutrients in AD may accelerate the loss of neuronal function. Also, the loss of neuronal function in AD may result in a greater need for specific nutrients to preserve remaining neuronal function. As the nutrient needs may be greater than for persons without AD, dietary modification alone may not result in adequate provision of these nutrients. Intervention points for maintaining neuronal function via medical foods may include β-amyloid protein processing, tau protein modification, synapse formation, inflammation, oxidative stress, mitochondrial energy production, blood-brain barrier maintenance, or a combination of these processes.[25] However, medical food developers for AD must provide rigorous scientific evidence, especially in humans, that these intervention points have unique nutritional needs that cannot be met with normal diet modification alone.

4. Clinical Trials Using Medical Foods for Alzheimer's Disease

Limited clinical trials have evaluated medical foods in patients with AD. Based on a PubMed search in January 2011 using the terms 'medical food' and 'Alzheimer', limiting the search to clinical trials published in English that included AD patients aged >65 years, and supplementing the search with other known articles meeting the inclusion criteria, only two medical foods, AC-1202[10] and Souvenaid® with Fortasyn Connect™,[26] were found to have results for discussion.

In March 2009, AC-1202 (Axona®; Accera, Inc., Bloomfield, CO, USA) was introduced in the US as a medical food for the nutritional needs of mild-to-moderate AD patients. Glucose hypometabolism by neurons has been associated with AD. However, neurons can use ketone bodies as an energy source when they have difficulties processing glucose, and medium chain triglycerides can be metabolized into ketone bodies. AC-1202 is a medium chain triglyceride product composed of glycerin and caprylic acid (C8:0). Caprylic acid is not present in sufficient quantities in regular dietary intake of coconut oil or palm kernel oil to meet the needs of persons with AD. After a meal, one packet containing 20 g of AC-1202 powder is shaken and blended in 4–8 oz (120–240 mL) of water and consumed immediately. The safety and efficacy of AC-1202 were evaluated in a randomized, double-blind, placebo-controlled, clinical trial conducted at multiple US centres that enrolled 152 participants, of whom the majority were already taking current FDA-approved AD treatments.[10] The primary outcomes were 90-day change in the Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-cog) score and on the Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (ADCS-CGIC) scale. The ADAS-cog score improved by a mean 0.31 points from baseline to day 90 in the group randomized to AC-1202 and worsened by a mean 1.23 points in the group randomized to placebo (p for group difference = 0.08). Changes from baseline in ADCS-CGIC scores by day 90 were not different between treatment and placebo groups (p = 0.35). In a pre-specified stratification analysis of participants without an apolipoprotein E (ApoE) ε4 allele, the 90-day ADAS-cog score improved by a mean 1.75 points in the treatment group while worsening by a mean 1.61 points in the placebo group (p = 0.01). Adverse event discontinuation rates were 23% in the treatment group versus 6% in the placebo group. The most common adverse events were gastrointestinal events (49% in the treatment group vs 27.3% in the placebo group). As ketone body production can be detrimental in conditions such as uncontrolled diabetes mellitus, intake of AC-1202 requires ongoing medical supervision. Instructions are necessary to reduce the gastrointestinal adverse effects that may be associated with intake of medium chain triglycerides. Given that AC-1202 may preferentially benefit individuals without an ApoE ε4 allele, genotype testing could be done as part of a medical evaluation. In practice, however, most clinicians suggest a short-term trial of AC-1202 and counsel patients that the medical food intervention can be stopped if no improvement is noted.

Another potential medical food with clinical trial data is Souvenaid® with Fortasyn Connect™ (Danone Research B.V., Wageningen, the Netherlands). Souvenaid® with Fortasyn Connect™ is a 125 mL (125 kcal) multi-nutrient drink for daily intake containing omega-3 fatty acids, phospholipids, choline, uridine monophosphate, vitamin E, vitamin C (ascorbic acid), selenium, vitamin B_{12}, vitamin B_6 (pyroxidine) and folic acid at levels above what can be achieved in the normal diet. The rationale for Souvenaid® with Fortasyn Connect™ is based on AD resulting in greater synaptic loss than synaptic production. Phosphatide molecules plus synaptic proteins comprise the bulk of synaptic membranes and can be increased by co-administration of rate-limiting precursors via the Kennedy pathway.[25] These rate-limiting precursors are provided in Fortasyn Connect™ in the vehicle of Souvenaid®. In a randomized, double-blind, multicentre European trial, 225 drug-naive, mild-to-moderate AD patients were randomized to once-daily intake of active product, i.e. Souvenaid® with Fortasyn Connect™, or placebo, i.e. Souvenaid® without Fortasyn

Connect™.[26] After 12 weeks, performance on the delayed verbal recall task of the Wechsler Memory Scale-Revised showed improvement in the treatment group compared with the placebo group ($p = 0.021$); however, the second primary outcome of score on the 13-item modified ADAS-cog subscale was unchanged. The adverse event discontinuation rate was 2.7% in the treatment group versus 3.6% in the placebo group. Adverse events were reported in 51% of the treatment group and 44% of the placebo group with the difference being not statistically significant. Gastrointestinal events were the most commonly reported adverse events (17.9% of the treatment group vs 18.6% of the placebo group). Based on the clinical trial safety data, it is unclear whether medical supervision is necessary for use of Souvenaid® with Fortasyn Connect™, which may place the intervention in the 'food with health claims' category rather than the 'medical food' category.

Interpretation of current medical food clinical trials is limited by having only a single study for a particular intervention, the small to medium number of AD participants evaluated, the short follow-up times for interventions that may have to be taken for many years, positive findings for some but not all primary outcomes, and limited comparisons with other approved treatments. Further studies are needed to overcome these limitations with AC-1202 and Souvenaid® with Fortasyn Connect™. For instance, an AC-1202 study powered to test the effect of ApoE allele status on the relationship between AC-1202 and cognitive outcomes using modification models rather than stratified models is important. For Souvenaid® with Fortasyn Connect™, determining if the intervention offers added benefit to AD patients already taking approved AD treatments is needed. A search of clinical trial registries revealed that a study examining the effects of AC-1202 on brain positron emission tomography is scheduled to start recruiting patients,[27] and a clinical trial of Souvenaid® with Fortasyn Connect™ in participants with mild-to-moderate AD already taking FDA-approved AD treatments is currently under way.[28]

A small number of additional medical foods aimed at meeting the specific nutritional needs of AD are undergoing clinical and pre-clinical testing. Zinc may be a synaptic neurotransmitter that modulates NMDA receptor activity and is a component of enzymes responsible for the degradation of β-amyloid. A 6-month, placebo-controlled, multicentre, phase II clinical trial is ongoing to determine whether zinc cysteine (Adeona Pharmaceuticals; Ann Arbor, MI, USA) affects serum copper and zinc levels and changes cognition in persons with AD or mild cognitive impairment.[29] Results are anticipated in 2011. In addition, pre-clinical work on a medical food cocktail of curcumin, piperine, epigallocatechin gallate, α-lipoic acid, *N*-acetylcysteine, B vitamins, vitamin C and folate (Akeso Health Sciences L.L.C.; Westlake Village, CA, USA) over 6 months in Tg2576 transgenic mice showed improved learning and decreased β-amyloid levels.[30]

5. Future Directions for Medical Foods for Alzheimer's Disease

Researchers, commercial developers, advocacy groups, government regulators, public and private healthcare payers, clinicians and patients will need to collaborate in order to define the appropriate level of scientific, ethical and regulatory standards necessary to justify the commercialization of future medical foods for AD. First, researchers must continue to examine whether AD has unique nutrient needs (which may differ for various disease stages) that cannot be met by modifying the normal diet alone. Second, researchers and developers need to consider the appropriate timing for introducing medical food interventions for AD patients. AD unfolds over the course of decades with a long asymptomatic phase, followed by a prodromal phase, and then followed by the presence of clinical manifestations. Third, AD advocacy groups will need to encourage medical food developers to provide the best scientific justification for recommending the use of a medical food.[31] Fourth, government regulators may need to consider requiring further confirmatory research regarding how a product commercially introduced as a medical food meets a unique nutritional need of AD patients. Establishing Recommended Dietary Intakes for new

micronutrients would also be helpful. Fifth, public and private healthcare payers should encourage the conduct of comparative effectiveness studies to support decisions about which AD interventions to cover. Finally, clinicians and patients need to foster the use of clinical tools to critically evaluate the efficacy, safety and tolerability of medical food interventions.

6. Conclusions

Medical foods may provide a unique platform for the development of AD interventions. One medical food for AD has been introduced in the US market and others are in development. A window of opportunity exists for establishing a comprehensive framework to ensure that medical food interventions for AD achieve the highest possible scientific, ethical and regulatory standards to warrant commercialization.

Acknowledgements

The preparation of this review was funded by the Illinois Department of Public Health Regional Alzheimer's Disease Assistance Center for Northeast Illinois Grant but was independent of the funders.

Dr Shah receives or has received research support as a principal investigator, site principal investigator, or sub-investigator for clinical trials of foods, dietary supplements, medical foods, and drugs in persons with normal memory, memory concerns, mild cognitive impairment, and Alzheimer's disease sponsored by Ceregene, Inc., Danone Research B.V., Eisai, Inc., Elan Pharmaceuticals, Inc., Merck & Co., Inc., Orasi, Inc., Pamlab, L.L.C., Pfizer, Inc., Takeda Global Research and Development Center, Inc., and the US National Institutes of Health.

References

1. Alzheimer's Disease International. World Alzheimer report 2009. London: Alzheimer's Disease International, 2009
2. Alzheimer's Disease International. World Alzheimer report 2010. London: Alzheimer's Disease International, 2010
3. Hansen RA, Gartlehner G, Webb AP, et al. Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. Clin Interv Aging 2008; 3 (2): 211-25
4. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev 2006 Jan 25; (1): CD005593
5. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane Database Syst Rev 2006 Apr 19; (2): CD003154
6. Silverberg GD, Levinthal E, Sullivan EV, et al. Assessment of low-flow CSF drainage as a treatment for AD: results of a randomized pilot study. Neurology 2002; 59 (8); 1139-45
7. Mangialasche F, Solomon A, Winblad B, et al. Alzheimer's disease: clinical trials and drug development. Lancet Neurol 2010 Jul; 9 (7): 702-16
8. Mandel RJ. Cere-110, an adeno-associated virus-based gene delivery vector expressing human nerve growth factor for the treatment of Alzheimer's disease. Curr Opin Mol Ther 2010 Apr; 12 (2): 240-7
9. Kelly BJ, Knopman DS. Alternative medicine and Alzheimer disease. Neurologist 2008 Sep; 14 (5): 299-306
10. Henderson ST, Vogel JL, Barr LJ, et al. Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial. Nutr Metab (Lond) 2009; 6: 31
11. US Food and Drug Administration. What is the difference between a dietary supplement and a conventional food? [online]. Available from URL: http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194357.htm. [Accessed 2010 Sep 27]
12. US Food and Drug Administration. Overview of dietary supplements [online]. Available from URL: http://www.fda.gov/Food/DietarySupplements/ConsumerInformation/ucm110417.htm [Accessed 2010 Sep 27]
13. US Food and Drug Administration. Claims that can be made for conventional foods and dietary supplements [online]. Available from URL: http://www.fda.gov/Food/LabelingNutrition/LabelClaims/ucm111447.htm [Accessed 2010 Sep 27]
14. US Food and Drug Administration. Medical foods: overview [online]. Available from URL: http://www.fda.gov/Food/FoodSafety/Product-SpecificInformation/MedicalFoods/default.htm [Accessed 2010 Sep 27]
15. US Food and Drug Administration. Guidance for industry: frequently asked questions about medical foods May 1997 – revised May 2007 [online]. Available from URL: http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/MedicalFoods/UCM054048 [Accessed 2010 Sep 27]
16. The Commission of the European Communities. Commission Directive 1999/21/EC of 25 March 1999 on dietary foods for special medical purposes. Official Journal L 091, 07/04/1999 P. 0029-0036 [online]. Available from URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31999L0021:EN:HTML [Accessed 2011 Jan 25]
17. The Commission of the European Communities. Commission Regulation (EC) No 953/2009 of 13 October 2009 on substances that may be added for specific nutritional purposes in foods for particular nutritional uses. Official Journal L 296, 14/10/2009 P. 0009-0019 [online]. Available from URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:269:0009:01:EN:HTML [Accessed 2011 Jan 25]
18. Sampson EL, Candy B, Jones L. Enteral tube feeding for older people with advanced dementia. Cochrane Database Syst Rev 2009 Apr 15; (2): CD007209
19. Wang PN, Yang CL, Lin KN, et al. Weight loss, nutritional status and physical activity in patients with Alzheimer's disease: a controlled study. J Neurol 2004; 251: 314-20

20. Cronin-Stubbs D, Beckett LA, Scherr PA, et al. Weight loss in people with Alzheimer's disease: a prospective population based analysis. BMJ 1997; 314: 178-9
21. Riviere S, Gillette-Guyonnet S, Voisin T, et al. A nutritional education program could prevent weight loss and slow cognitive decline in Alzheimer's disease. J Nutr Health Aging 2001; 5: 295-1259
22. Gillette-Guyonnet S, Nourhashemi F, Andrieu S, et al. Weight loss in Alzheimer disease. Am J Clin Nutr 2000; 71: S637-42
23. Tamura BK, Masaki KH, Blanchette P. Weight loss in patients with Alzheimer's disease. J Nutr Elder 2007; 26: 21-38
24. Ferreira IL, Resende R, Ferreiro E, et al. Multiple defects in energy metabolism in Alzheimer's disease. Curr Drug Targets 2010; 20: 1193-206
25. Kamphuis PJ, Scheltens P. Can nutrients prevent or delay onset of Alzheimer's disease? J Alzheimers Dis 2010; 20: 765-75
26. Scheltens P, Kamphuis PJ, Verhey FR, et al. Efficacy of a medical food in mild Alzheimer's disease: a randomized, controlled trial. Alzheimers Dement 2010; 6: 1-10.e1
27. Grill J. A positron emission tomography (PET) study evaluating brain metabolism of a medical food in Alzheimer's disease (AD) [ClinicialTrials.gov identifier NCT01122329]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: http://www.clinicaltrials.gov [Accessed 2010 Oct 2]
28. Danone Research BV. A randomized controlled trial to assess the efficacy of a food in patients with mild to moderate Alzheimer's disease using Alzheimer's disease medication (TrialRegister.nl identifier NTR1683) [online]. Available from URL: https://www.trialregister.nl [Accessed 2010 Oct 2]
29. Newsome D. Copperproof-2: prospective, randomized, double-blind placebo-controlled clinical trial comparing the effects of a novel once-daily oral zinc cysteine preparation on zinc and copper parameters in mild cognitive impairment and Alzheimer's disease [ClinicialTrials.gov identifier NCT01099332]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: http://www.clinicaltrials.gov [Accessed 2011 Jan 25]
30. Parachikova A, Green KN, Hendrix C, et al. Formulation of a medical food cocktail for Alzheimer's disease: beneficial effects on cognition and neuropathology in a mouse model of the disease. PLoS ONE 2010; 5 (11): e14015
31. Alzheimer's Association. Medical foods [online]. Available from URL: http://www.alz.org/national/ documents/statements_medicalfoods.pdf [Accessed 2010 Sep 30]

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