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Use of medical foods and nutritional approaches in the treatment of Alzheimer's disease

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SUMMARY

Alzheimer's disease, the most common cause of dementia, has a high global economic impact. To date, there is no curative treatment; therefore, many efforts are directed not only at novel potential disease-modifying treatments and interventions, but also to develop alternative symptomatic and supportive treatments. Examples of these efforts include the medical foods. There are three medical foods that claim to offer symptomatic benefits: Axona[®], Souvenaid[®] and CerefolinNAC[®]. Axona supplies ketone bodies as alternative energy source to neurons. Souvenaid provides precursors thought to enhance synaptic function. CerefolinNAC addresses the role of oxidative stress related to memory loss. The current scientific evidence on these medical foods is reviewed in this article. Furthermore, we also review the concept and evidence supporting use of the Mediterranean diet, a possible alternative to medical foods that, if implemented correctly, may have lower costs, fewer side effects and stronger epidemiological health outcomes.

Alzheimer's disease (AD) is the most common cause of dementia, affecting over 5 million North Americans and 14 million individuals worldwide [1]. In its early stages, AD affects predominantly short-term memory and language ability, with progressive changes in cognition, function, mood and behavior, resulting in increased caregiver burden [2]. In 2010, the global economic impact of dementia was estimated to be US\$604 billion. This figure dwarfs the costs of cancer or heart disease [3]. Based on demographics, the Alzheimer's Disease International (ADI) foresees an 85% increase in cost by 2030, with the developing countries bearing an increasing share of the disease burden [3]. At present, only symptomatic treatment is available for AD in the USA, comprised of four acetylcholinesterase inhibitors (tacrine, donepezil, rivastigmine and galantamine) and one glutamate receptor antagonist (memantine). While these medications offer modest benefit, they are not curative [4]. Thus, there is active research to develop novel approaches to AD treatment with the hopes of either modifying disease pathophysiology or enhancing cognitive function with alternative approaches. One such approach currently available is the use of medical foods and dietary modifications.

Medical foods were defined in 1988 as a special category of products intended for the specific dietary management of a disease or condition that has distinctive nutritional

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requirements, established by medical evaluation and based on recognized scientific principle [101]. The US FDA criteria for a medical food are [5]:

- A specially formulated and processed product for the partial or exclusive feeding of a patient by means of oral intake or enteral feeding by tube;
- 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;
- 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;
- Intended to be used under medical supervision.

The characteristic of a medical food is that it is expected to be used under the regular care of a physician, so patients who are interested in using this type of material should discuss it carefully with their own physician and make sure that they, the physician and the family understand the appropriate use, realistic treatment expectations and potential adverse effects. Before discussing the currently available products, it is important to note that the FDA does not require the same high level of testing for approval of medical foods as it does for prescription medications. This may be particularly true when considering supplements that are often confused with medical foods, leaving patients and their families potentially vulnerable to unproven claims. Supplements are not regulated by the FDA, are meant for healthy individuals and are not intended to diagnose, treat or manage disease or disease symptoms [102]. Medical foods and to a lesser extent supplements are not replacements for prescription medications; however, used alongside pharmacological approaches under a physician's supervision, both can enhance patient care.

There are three medical foods that claim to have benefits for use in dementia patients and are available in the USA and/or Europe: Axona[®] (AC-1202, Accera, Inc., CO, USA) [6], Souvenaid[®] (Danone Research, France) [7] and CerefolinNAC[®] (LA, USA) [103]. The goal of this article is to review the current scientific evidence of these medical foods in treating AD (Table 1). We also discuss the evidence available for the Mediterranean diet, a nonmedical food dietary approach that may alleviate the symptomatic burden of AD.

Axona

Known by the brand name 'Axona', this medical food composed of a proprietary formulation of caprylic acid proposes to target metabolic deficiencies associated with AD [6]. The product was launched by Accera in 2009. In AD, there is a characteristic cerebral hypometabolism on fluorodeoxyglucose PET scans that can be used to assist in diagnosis [8]. Cerebral perfusion is progressively decreased owing to aging and vascular risk factors and is significantly greater in AD, particularly in the temporal–parietal region [9]. Cerebral hypoperfusion may induce brain capillary degeneration and suboptimal delivery of energy substrates, such as glucose, to neural tissue. This may compromise neural stability and metabolic cascades, for example, mitochondrial dysfunction, oxidative stress and neurotransmission failure, leading to progressive cognitive decline characteristic of AD, as well as synaptic loss, senile plaques, neurofibrillary tangles, tissue atrophy and neurodegeneration [9]. This decrease in ability to utilize glucose contributes to the clinical and pathological course of disease [10]. Axona is a medium-chain triglyceride product composed of glycerin and caprylic acid, which is metabolized to the ketone body β -hydroxybutyrate (BHB) in the liver, providing neurons with an alternative energy source to

glucose (Figure 1) [11]. Caprylic acid contains 12 carbons and is entirely metabolized by the liver to BHB without associated changes in serum cholesterol or triglyceride levels [6]. The ketone body BHB crosses the blood–brain barrier and enters the neurons, localizing in mitochondria. Inside the mitochondria, BHB is metabolized into acetyl coenzyme A by a simple three-step process. Acetyl coenzyme A then enters the citric acid cycle, leading to production of ATP. BHB metabolism also generates nicotinamide adenine dinucleotide and succinate substrates for complexes of the mitochondrial electron transport [104]. Axona is administered orally once a day, and is supplied as a powder to be mixed with water or other foods/liquids for immediate consumption [6].

As described above, AD patients have a progressive, region-specific decline in the cerebral metabolic rate of glucose [12], especially in posterior cingulate, parietal, temporal and prefrontal cortices, which occurs early in the course of AD even before the demonstration of cell loss [13]. Normally, glucose is the main energy substrate for the brain, but under certain circumstances, such as the fasting period, ketone bodies from the liver can serve as alternative sources of energy [14]. Results from a mouse model suggest that induced ketosis may be beneficial in AD [15]. Another small study of 23 older adults with mild cognitive impairment who received either a high carbohydrate or very low carbohydrate (ketogenic) diet for 6 weeks showed improvement on verbal memory performance in the ketogenic group. This study also demonstrated that ketone body levels were positively correlated with memory performance [16]. These preliminary studies support the idea that ketone bodies may provide symptomatic benefit as an alternative source of energy to AD patients.

At the Alzheimer's Association 2007 International Conference on Prevention of Dementia, the company presented findings from a Phase II double-blind, randomized, multicenter, placebo-controlled trial of 152 patients with probable mild-to-moderate AD. Results of the trial showed those taking Axona had significant improvement in the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) at day 45 ($p = 0.024$), which was maintained through day 90, although the difference was no longer significant at that point ($p = 0.0767$). The difference in ADAS-cog was significant at both day 45 ($p < 0.0005$) and day 90 ($p = 0.015$) in a subset of *APOE ε4*-negative patients [17].

Adverse event discontinuation rates were 23% in the treatment group and 6% in the placebo group [17]. The most common adverse events were diarrhea, flatulence and dyspepsia. No significant interactions were seen with commonly prescribed AD drugs, including donepezil and/or *N*-methyl-D-aspartic acid-receptor agonists such as memantine.

The product contains caseinate, whey and lecithin, but is lactose free. The company recommends that it should be used with caution in patients with known hypersensitivity to palm or coconut oil, those at risk for ketoacidosis, or those with a history of gastrointestinal inflammation, metabolic syndrome and/or a history of renal dysfunction [6]. Axona should be consumed after a full meal.

Souvenaid

Souvenaid is a medical food that may soon be available in the US market. The product, a 125-ml (125-kcal) once-daily drink, combines a variety of substrates including uridine monophosphate, phospholipid, choline and omega-3 fatty acids, vitamins and antioxidants, which are thought to be essential for formation of synaptic membranes [105]. Although all of Souvenaid's constituents can be found in food, none of the uridine contained in the average adult dietary sources is bioavailable [18]. Souvenaid contains the necessary precursor and supporting nutrients thought to act synergistically to enhance membrane formation and function in patients with AD (Figure 2) [19]. The brains of Alzheimer's patients show evidence of synaptic failure [20,21]. Deficiency in synapses is both one of the

earliest manifestations of AD as well as the probable cause of cognitive disturbance observed in the early course of disease [21]. Souvenaid's constituents may be involved in generation of new synaptic connections such as dendritic spine growth [22]. Uridine may help to promote neurite branching, neurite protein synthesis and stimulate neuritogenesis by activation of brain P2Y receptors that control neuronal differentiation [23]. 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 [19].

The multicentered trial, including both European and US sites, was published in 2010 [7]. This trial included 225 drug-naïve patients with baseline Mini-Mental State Examination scores of 20–26. Patients were randomized to receive Souvenaid or a placebo drink once daily for 12 weeks. The study's primary outcome measures were the delayed verbal recall task on the Wechsler Memory Scale-Revised and the 13-item modified ADAS-cog scale.

At 12 weeks, the investigators found significant improvement in Wechsler Memory Scale-Revised delayed verbal recall scores in the Souvenaid group compared with the placebo group ($p = 0.021$). However, there was no change in ADAS-cog scores in either group [7]. The compound was well tolerated and there was no significant difference in the incidence of adverse events between the study groups. Furthermore, most of the adverse events were deemed unrelated to the study products. 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. Gastrointestinal events were the most commonly reported adverse events [5–7].

This was followed by a 3-month extension period during which patients could choose to continue with the double-blind regimen or begin taking open-label Souvenaid. Approximately 85% of subjects chose to continue with the double-blind regimen, providing the investigators with 6 months of data. Results from the extension study, published recently [24,25], indicated that a higher treatment effect ($p = 0.046$) was shown in patients with high-baseline ADAS-cog, but not in patients with low-baseline ADAS-cog. Overall, intake adherence was significantly correlated with ADAS-cog improvement in the Souvenaid group, but not in the control group [24]. The extension study also included BMI and the 23-item Alzheimer's Disease Cooperative Study-Activities of Daily Living scale as secondary outcomes. Results suggested an increased BMI in the Souvenaid group versus the control group at week 24, but no treatment effect on Alzheimer's Disease Cooperative Study-Activities of Daily Living was observed. Furthermore, BMI was found to be a significant treatment effect modifier and an increase in Alzheimer's Disease Cooperative Study-Activities of Daily Living was observed in week 12 in patients with low-baseline BMI [25].

The second clinical trial of Souvenaid was presented at the 4th International Conference on Clinical Trials in Alzheimer's Disease, CA, USA, in November 2011. The study included 259 patients with early AD (Mini-Mental State Examination score average of 25), who received Souvenaid or placebo daily for 24 weeks. As much as 91% of patients finished the study. Memory was tested at the beginning, at 12 weeks and at 24 weeks. The composite score was taken from the Rey Auditory Verbal Test, which examines instant recall, delayed memory and recognition. The Wechsler Scale was also carried out to test verbal association. Results showed the total scores from the Souvenaid group were significantly higher than the control group ($p = 0.025$) and no differences between frequency of adverse events were observed between the two groups [106].

CerefolinNAC

CerefolinNAC ingredients consist of methylcobalamine 2 mg (vitamin B12), L-methylfolate 5.6 mg and N-acetylcysteine 600 mg; it can be taken with or without food [103]. It is

approved by the FDA for the treatment or prevention of vitamin deficiencies associated with memory loss. The package insert also claims that CerefolinNAC addresses metabolic and genetic nutritional impairments associated with memory loss that can lead to AD. This is somewhat different from Axona and Souvenaid, which target a proposed mechanism of action relevant to those who are diagnosed with AD [107]. There is a body of literature suggesting that the reduction of blood levels of homocysteine may reduce risks of vascular disease such as heart attacks and stroke [26–28]. This may be accomplished with supplementation of B vitamins involved in homocysteine metabolism [108]. However, two meta-analyses of effects of folic acid, with or without other B vitamins, on the prevention of cognitive decline in memory-impaired patients both did not find any benefit of folic acid with or without vitamin B over placebo [29,30]. In addition, an Alzheimer Disease Cooperative Study of folate and B12 for the symptomatic benefit of AD failed to reach primary end points [31]. One possible advantage of using CerefolinNAC over other B-vitamin supplements is that it contains formulations of folic acid and vitamin B12, which are thought to be ‘active’, suggesting that they are ready to use by the body without the need for conversion [103]. This is further supported by the recent VITACOG clinical trial, which supplied high levels of folate, B12 and B6 to 271 elderly subjects with MCI, to evaluate ability of homocysteine-lowering B vitamins to arrest brain atrophy. The investigators found that only patients with the highest quartile of baseline homocysteine had benefit on brain atrophy by 53% with vitamin B treatment for 24 months. No effect was found in those with the lower quartile on baseline homocysteine [32]. Thus the level of homocysteine reduction may be critical to demonstration of clinical benefits.

CerefolinNAC’s therapeutic approach is addressing homocysteine and oxidative stress linked to progressive memory loss (Figure 3). Although the etiology of AD is evolving, some studies have demonstrated that oxidative stress plays a role in disease pathophysiology [33,34] including the fact that amyloid deposition is able to induce and be induced by oxidative stress [35]. Over time, oxidative damage is likely to be toxic to neurons. Several byproducts of protein, lipid and glucose oxidation appear to be elevated in the brains of AD patients compared with healthy controls; this may be a result of the burden of free radicals accumulating proportionally to the duration of the disease [36,37]. The brain’s unique characteristics, including its high rate of metabolism and its long-living cells, make it more susceptible to oxidative damage compared with other organs [38]. The human body has an antioxidant defense system to help regulate oxidative stress [39]. Antioxidants block the process of oxidative stress by neutralizing free radicals; however, endogenous antioxidant resources are depleted with age, so there is a constant need to replenish them [37]. *N*-acetylcysteine increases the body’s production of glutathione, which is the brain’s most important scavenger of reactive oxidative species, also known as free radicals [40]. A report on several case studies has shown oral supplementation with NAC, in addition to folate and vitamin B12 therapy, may reduce the effects of oxidative stress and improve cognitive function in patients with memory deficits [41].

Elevated homocysteine levels may result from abnormalities in the function of enzymes involved in homocysteine metabolism or from deficiencies of the vitamin cofactors: folate, cobalamin (B12) and pyridoxine HCl (B6) [108]. Elevated homocysteine is hypothesized to be a risk factor for vascular disease. Although American Heart Association guidelines do not recommend widespread use of folic and vitamin B supplements to reduce the risk of heart disease and stroke, the guidelines do suggest eating a healthy and balanced diet, which contains 400 µg of folic acid per day [109]. Folic acid and other B vitamins are important cofactors for metabolism of homocysteine, thus homocysteine levels may be strongly influenced by a combination of dietary and genetic factors [109]. Elevated blood homocysteine may also be a useful marker for neuroinflammation. In AD, elevated homocysteine can be lowered by folic acid plus B-vitamin supplements and *N*-

acetylcysteine [40]. However, the recent systemic meta-analysis and meta-regression review of causative links between high homocysteine and AD did not support a causal relationship, even though individuals with AD had higher homocysteine level than controls [42].

Results from a 1-year uncontrolled open study of a nutraceutical formulation containing folic acid, B12 (*N*-acetylcysteine (constituents of CerefolinNAC), as well as vitamin E, *S*-adenosylmethionine and acetyl-L-carnitine, in 14 patients with early-stage AD indicated improvements in the Dementia Rating Scale and Clock-drawing tests, multiple domains of the Neuropsychiatric Inventory and maintenance of performance in the Alzheimer's Disease Cooperative Study-ADL [43]. Although CerefolinNAC lacks the randomized clinical trial-based evidence provided by Axona and Souvenaid, complementary studies with constituents suggest high doses of folate sufficient to lower homocysteine offer a clinical benefit.

According to the package insert, a single dose of L-methylfolate 5 mg is three-times more effective in decreasing plasma homocysteine compared with folic acid 5 mg and C_{max} is also higher (129 vs 14.1 ng) [103].

Common adverse reactions of CerefolinNAC include mild transient diarrhea, polycythemia vera, itching, transitory exanthema and the feeling of swelling of the entire body, which have been associated with methylcobalamin. Nausea, vomiting, headache, other gastrointestinal symptoms and rash (with or without mild fever) have been associated with CerefolinNAC. In addition, there are rare reports of renal stone formation with CerefolinNAC [103].

Mediterranean diet

The Mediterranean diet does not comprise of medical foods, however, the concept is very similar to medical food whereby a specific healthy dietary pattern is adhered to, which may help in the prevention or delay of AD progression. There are a number of dietary approaches and interventions that have been proposed for the prevention and/or treatment of AD. We included a single dietary approach (i.e., the Mediterranean diet) and its scientific evidence to give one example of possible alternative nutritional approaches that may have lower costs, lower side effects and stronger epidemiologic evidence of health outcomes.

The most common version of the Mediterranean diet was presented by Dr Walter Willett of Harvard University's School of Public Health in the mid-1990s [44]. This diet emphasizes plant-based foods in abundance, fresh fruit as the typical daily dessert, olive oil as the principal source of fat, dairy products (principally cheese and yogurt), fish and poultry consumed in low to moderate amounts, zero to four eggs consumed weekly, red meat consumed in low amounts and wine consumed in low to moderate amounts. The total fat in this diet is 25–35% of daily calorie allowance, with saturated fat at 8% or less of daily calorie allowance [44].

A number of published studies found the benefits of adhering to the Mediterranean diet are being less likely to develop depression [45], more than 50% lowering of early death rates [46] and 83% relative reduction in the risk of developing diabetes [47]. The Seven Countries Study report also found the Cretan diet – a type of traditional Mediterranean diet consisting mostly of olive oil, bread, an abundance of fruits and vegetables, fish and moderate amounts of dairy foods and wine – can help lower death rates from heart disease [48]. The Lyon Diet Heart Study was a randomized, controlled trial with free-living subjects. Its goal was to test the effectiveness of a Mediterranean-type diet on the rate of coronary events in people who have had a first heart attack. A total of 302 experimental and 303 control subjects were randomized in the study. The results suggest that a Mediterranean-style diet may help reduce recurrent events in patients with heart disease [49]. The Mediterranean diet is low in

saturated fat and high in monounsaturated fat and dietary fiber. The possible explanations for the results may include the healthy effect of olive oil on the heart, or the consumption of red wine containing flavonoids with powerful antioxidant properties [50]. Following the concept of ‘what is good for the heart is good for the brain’, the Mediterranean diet has been increasingly studied in patients with AD and in individuals at risk for dementia.

A Washington Heights–Inwood Columbia Aging Project (WHICAP) was the first to report a beneficial effect of the Mediterranean diet on incidence of AD [51]. Over 2000 individuals older than 65 years of age had a complete assessment of cognitive functions and dietary habits and were followed-up for an average of 4 years. The study found that higher adherence to the Mediterranean diet was significantly associated with a lower risk of development of AD, even after adjustment for age, sex, ethnicity, education, *APOE* genotype, caloric intake, smoking, comorbidity index and BMI. Compared with individuals in the lowest tertile of the Mediterranean diet score (score 0–3; indicating a low adherence to the Mediterranean diet), those in the middle score tertile (score 4–5) had 21% less risk for development of AD and those in the highest tertile (score 6–9; indicating a high adherence to the Mediterranean diet) had 40% less risk for development of AD, with a trend for a dose–response effect, in fully adjusted models [51]. Furthermore, among individuals who had MCI at baseline, adherence to the Mediterranean diet had a significantly reduced risk of developing AD over time [52].

Another prospective study was the Three-City Study from France [53]. A prospective cohort study of 1410 individuals aged 65 years or older, who were free from dementia at baseline, then followed-up at least once over a period of 5 years. The main original finding was that higher adherence to the Mediterranean diet was significantly associated with better global cognitive performance and episodic memory over time, especially in individuals who remained free from dementia. Nevertheless, there was no association between the adherence to the Mediterranean diet and risk of dementia or AD in older individuals in this study [53]. Another recent study from the Mayo Clinic (MN, USA) also found that the odds ratio of MCI was reduced for high vegetable intakes and high mono- plus poly-unsaturated fatty acid to saturated fatty acid ratio [54].

A meta-analysis of eight prospective studies analyzed the relationship between adherence to a Mediterranean diet, mortality and incidence of chronic disease in a primary prevention setting. The authors found that adherence to the Mediterranean diet is associated with a significant improvement in health status, as seen by a significant reduction in overall mortality (9%), mortality from cardiovascular diseases (9%), incidence of or mortality from cancer (6%) and incidence of Parkinson’s disease and AD (13%). These results seem to be clinically relevant for public health, in particular, for encouraging a Mediterranean-like dietary pattern for primary prevention of major chronic diseases associated with aging [55].

Conclusion

There is increasing interest in alternative ‘natural’ approaches to treating AD in addition to the current regimen of pharmacologic approaches. This has spurred the development of medical foods to overcome metabolic deficits or address dietary deficiencies that have been associated with AD.

CerefolinNAC and Axona are the two medical foods that are currently available by prescription. CerefolinNAC’s therapeutic approach of addressing homocysteine levels and oxidative stress might benefit a variety of patients with cognitive disorders; however, more systematic studies are needed to confirm efficacy. All references in the package inserts are limited to case reports or case series. Randomized clinical trials examining folate

supplementation (with or without B12 supplementation) have failed to demonstrate any benefit. Axona's approach of providing an alternative energy source (ketone bodies) to the brain other than glucose demonstrates clinical benefit only in the specific group of *APOE* $\epsilon 4$ -negative patients. A larger and longer Phase III study will help clearly determine its benefit, since the preliminary study was a relatively short 90-day trial compared with most AD trials, which last at least 26 weeks with open-extensions of 1 year or longer. The lack of benefit when measuring ADAS-cog in *APOE* $\epsilon 4$ -positive group leads to some question on how to best select the patient in clinical practice because *APOE* genotype testing is not routinely done. The last medical food that may soon be available is Souvenaid, where preliminary data have shown some improvement in verbal recall task, but not in the general cognitive scale. Published studies report a trial that is of short duration, double-blind for 12 weeks, with an extension period of 12 weeks. At baseline, approximately 40% of enrollees scored 0, the lowest score on the delayed verbal recall test (Wechsler Memory Scale-Revised) – one of the two primary outcome measures. This skew in study population required the authors to use a nonparametric analysis, instead of the planned parametric assessment. A recent presentation of a second randomized clinical trial supports the clinical benefit of Souvenaid.

Future perspective

Preliminary studies of medical foods have largely been conducted in mild AD, so results cannot be generalized to all stages of AD. The potential benefit of medical foods in MCI is also unclear. An important issue to reiterate is that the FDA does not require the same high level of testing for approval of medical foods as it does for prescription medications. The efficacy demonstrated so far for medical foods is at best comparable with current symptomatic medications and then so only in select populations. Medical foods are generally considered safe and have a minimal side-effect profile compared with drugs; however, careful use after a discussion about risks and benefits with the physician is still recommended. At the present, the prescription of medical foods should be considered as an adjunct to and not a replacement for current medication use.

Finally, there is increasing evidence that specific dietary patterns, especially the Mediterranean diet, show promise for reducing the risk of developing dementia as well as reducing symptom burden after diagnosis. Although challenging, the Mediterranean diet can be adopted into many diets. Many medical foods are founded on sound nutritional principles and current hypotheses of disease, but larger clinical studies are needed to fully establish efficacy. What is clear is that the concept of 'what is good for the heart is good for the brain' may be particularly true when considering nonpharmacological approaches to AD and other diseases of the aging brain.

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Practice Points

- General definition and availability: medical foods are a special category of products intended for special dietary management of diseases or conditions that have distinctive nutritional requirements or metabolic deficiencies, based on medical evaluation and scientific principles. Their ingredients are generally regarded as safe. Currently, there are three medical foods that claim to have benefit for Alzheimer's disease (AD) and memory impairment: Axona[®], Souvenaid[®] and CerefolinNAC[®].
- Axona and its scientific evidence: Axona provides neurons with an alternative energy source to glucose, the ketone body β -hydroxybutyrate. Evidence from a Phase II multicenter randomized clinical trial (RCT) showed significant improvement in cognitive testing (measured by the Alzheimer Disease Assessment Scale-cognitive subscale) at 90 days in APOE ϵ 4 allele-negative patients.
- Souvenaid and its scientific evidence: Souvenaid contains precursors and supporting nutrients thought to enhance membrane and synaptic formation and function in AD. Evidence from a multicenter RCT showed improvement in a verbal recall task, but not Alzheimer Disease Assessment Scale-cognitive subscale in mild dementia at 12 weeks.
- CerefolinNAC and its scientific evidence: CerefolinNAC addresses hypotheses regarding the role of homocysteine and oxidative stress related to memory loss that may lead to AD. Evidence is largely limited to case reports reporting benefits.
- A Mediterranean diet and its scientific evidence: the Mediterranean diet is not strictly medical food, but has a similar concept of using dietary patterns to help prevent or delay the onset and symptoms of AD. Evidence from two RCTs showed adherence to the Mediterranean diet had a reduced risk of AD and better global cognitive performance. A meta-analysis also found that adherence to the Mediterranean diet reduced incidence of AD by 13% as well as overall mortality owing to AD.
- Medical foods and their practical points and limitation: all three medical foods are relatively new to the market. More extensive RCT studies will provide clearer information on the benefit of each product. Medical foods are not meant to replace commonly prescribed medications, but rather to be used in conjunction with medication as adjuvant therapies.

Figure 1.
Proposed mechanism of action of Axona®.
BHB: β -hydroxybutyrate.

Figure 2.
Proposed mechanism of action for Souvenaid®.

Figure 3.
Proposed mechanism of CerefolinNAC®.

Table 1

Supporting evidence for medical foods and the Mediterranean diet to treat Alzheimer's disease.

Medical foods	Evidence to support the benefits in dementia
Axona®	Phase II multicenter RCT showed significant improvement of ADAS-cog at 90 days in <i>APOE ε4</i> -negative patients
Souvenaid®	Multicenter RCT showed improvement in verbal recall task on WMS-R, but not ADAS-cog in mild dementia at 12 weeks
CerefolinNAC®	Case studies report supplement of CerefolinNAC to folate and B12 may improve cognitive function. However, two meta-analysis studies of effect of folic acid, with or without vitamin B, on the prevention of cognitive decline in memory impairment patients both did not find any benefit of folic acid with or without vitamin B over placebo
Mediterranean diet	Two RCTs showed those who adhered to the Mediterranean diet had significantly less risk of Alzheimer's disease, and better global cognitive performances. Meta-analysis found adherence to Mediterranean diet reduced overall mortality and incidence of Alzheimer's disease (13%)

ADAS-cog: Alzheimer's Disease Assessment Scale-Cognitive; RCT: Randomized clinical trial; WMS-R: Wechsler Memory Scale-Revised.