Reversal of Alzheimer’s Disease and Optimization of Brain Health with Orthomolecular Medicine

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Abstract
The treatment of Alzheimer’s disease (AD) is one of the greatest medical failures in recent times. Monotherapeutic pharmaceutical drug therapies have been grossly unsuccessful and this failure calls for a reappraisal of the clinical approach and consideration that multi-component nutritional and lifestyle–medicine based interventions that target the many underlying mechanisms may be required for optimal clinical outcomes. Indeed, a personalized nutritional and lifestyle medicine-based model may represent a more effective therapeutic approach as it has the potential to address the multitude of pathological factors that give rise to AD. As a model for personalized nutrition, orthomolecular medicine has the potential to provide a clinical and research framework for the reversal of Alzheimer’s disease and optimization of brain health.

Introduction
Alzheimer’s disease (AD) is a progressive neurodegenerative disorder that occurs slowly and results in memory loss, behavior changes, and cognitive decline (Parihar, 2004). More specifically, AD related dementia is characterized by progressive memory loss over months to years with the gradual emergence of executive, language, visuospatial, and other deficits with or without behavioral features (McKhann, 2011). The estimated prevalence of AD is 30 million people worldwide, a number that is expected to quadruple in 40 years, making it the most common form of dementia and one of the greatest medical challenges in the 21st century (Holtzman, 2011).
The pathology of AD broadly involves the accumulation of proteins, loss of neurons and synapses, and alterations related to reactive processes such as inflammation and loss of plasticity, and is characterized by the defining pathologic feature of amyloid plaques and neurofibrillary tangles (Duyckaerts, 2009). Notably the pathophysiological process of AD is now recognized to be evident decades before clinical symptoms of AD dementia, and this "preclinical" phase represents a critical opportunity for therapeutic intervention (Sperling, 2011).

The marked failure of monotherapeutic drug therapies for AD has called for a reappraisal of the clinical approach, with the suggestion that multi-component interventions that target the many underlying mechanisms may be required for optimal clinical outcomes (Bredesen, 2011). Indeed, a personalized lifestyle medicine-based model may represent a more effective therapeutic approach as it has the potential to address the multiple factors that give rise to AD (Bland, 2016).

A comprehensive personalized approach for the reversal of cognitive decline, the metabolic enhancement for neurodegeneration (MEND) program, that incorporates lifestyle, dietary, orthomolecular, and functional medicine-based interventions has been developed and shown success in reversing – not just preventing – cognitive decline in patients with AD (Bredesen, 2014, Bredesen, 2015). Evidence that personalized lifestyle medicine may be an effective preventative and treatment for AD is compatible with the emerging view that the diverse pathological events that underlie neurodegeneration are secondary to modifiable pathophysiological phenomena and upstream causes (Nehls, 2016).

Orthomolecular psychiatry is a framework for improving mental health through establishing an optimal physiological environment for brain function by considering an individual's unique genetic predisposition, biochemistry, and nutritional intake and requirements (Pauling, 1968). In a clinical setting, the practice of orthomolecular psychiatry is typically concerned with the optimization of physiological function through personalized nutrition and is supported by considerable (Beric, 2014). The following narrative review captures emerging clinical science that supports the notion that an orthomolecular medicine-based approach has the potential to reverse – not simply prevent – AD by improving physiological and neurological function.

Diet and the Alzheimer's Brain

Diet is a potent modifier of neurological function and plays a strong role in the development of AD, in addition, dietary therapy is also emerging as a therapy for AD prevention and treatment. Diets typical of industrialized cultures that are high in ultra-processed foods can impair cognition in healthy subjects within days and are a strong risk factor for dementia and AD over longer periods of time (Beilharz, 2015). Direct mechanisms by which unhealthy food can give rise to dementia and Alzheimer’s disease include oxidative stress, neuroinflammation, increased blood brain barrier permeability, reduced neurotrophic factors, and insulin resistance (Beilharz, 2015). In contrast, healthful dietary patterns have been associated with improved cognitive function and lower Alzheimer’s disease risk (Petersson, 2016). And dietary intervention studies have suggested rapid (in days) improvements in cognitive function in healthy subjects (McMillan, 2011), and gradual (over months to years) improvement in high risk adults (Smith, 2010, Martínez-Lapiscina, 2013). Several types of dietary interventions have been explored in people with dementia and AD, with the traditional Mediterranean-style diet and the “MIND diet” currently amongst the most promising.

Intervention with a traditional Mediterranean-style diet (supplemented with either extra-virgin olive or mixed nuts) was found in a secondary analysis of a cardiovascular prevention trial to significantly improve measures of cognitive function, including the Mini-Mental State Examination (MMSE) after 6.5 years (Martínez-Lapiscina, 2013). A similar study of a traditional Mediterranean-style diet supplemented with olive oil or nuts in a cardiovascular high-risk older population was also found to improve cognitive function after 4.1 years (Valls-Pedret C, 2015). In contrast, one study reported no benefit, however, it was a smaller sample size and shorter study length of 6-months (Knight, 2016).
A diet that has been specifically developed for protection of the brain, called the MIND (Mediterranean-DASH Diet Intervention for Neurodegenerative Delay) diet, has been strongly associated with slower cognitive decline and risk of AD, with a greater estimated effect than the Mediterranean diet (Morris, 2015, Morris, 2015b). The unique features of the MIND diet are based on evidence for foods and nutrients associated with dementia prevention, including consumption of green leafy vegetables and berries while not specifying high fruit, dairy, or potato consumption or greater than 1 fish meal per week. A clinical trial of the MIND diet is currently underway (Morris, n.d.).

Modification of Excessive Oxidative Stress

An imbalance between the production of active reactive oxygen species (ROS) and antioxidant activity can result in cell damage and neurodegeneration (Gandhi, 2012). Oxidative stress is the net result of this imbalance and has been implicated in the development of AD (Zhao, 2013). Epidemiological studies of dietary antioxidants have suggested a protective effect, yet clinical trials of nutritional antioxidant therapies have generally been met with little success, however, this may be due to factors such as inadequate study duration, inappropriate choice of antioxidant intervention, use of single molecules instead of complex interventions, and failing to select individuals with low antioxidant and/or high oxidant activity at baseline (Praticò, 2008).

Reduced levels of exogenous antioxidants, especially vitamin C, vitamin E and selenium, have been documented AD patients (Thapa, 2017). There is some evidence to suggest that optimizing intake of these and other antioxidant nutrients may help reduce risk of cognitive decline, especially when personalized to those with biochemical evidence of low nutritional status or higher metabolic demands of these nutrients (Monacelli, 2017, Cervantes, 2017, Cervantes, 2016). Additionally, optimizing dietary intake of a diverse range of plant-foods such as fruits, vegetables, herbs and spices and their antioxidant phytochemicals has been proposed as a logical strategy for AD treatment and prevention (Thapa, 2017). Indeed, dietary intervention has been shown to be a powerful modulator of central nervous system oxidative stress in adults, including those with mild cognitive impairment (Bayer-Carter, 2011).

Improving Mitochondrial Function

Mitochondrial dysfunction is well documented in human AD subjects, both within the brain and systemically, and is thought to play a primary role in the development of the disease via generation of excessive oxidative stress, contribution to neuroinflammation and subsequent increase in amyloid beta production (Wilkins, 2017). Improving mitochondrial function, so called mitochondrial medicine, is emerging as an important consideration in the clinical management of AD with specific diets and dietary supplements amongst the most promising strategies (Wilkins, 2016).

Potential nutritional strategies for improving mitochondrial function include increasing dietary intake of “neurohormetic” phytonutrients from plant food sources as well as the use of specific natural supplements (Murugaiyah, 2015, Akbar, 2016, Nicolson, 2014) . Dietary approaches under investigation for improving brain bioenergetics include ketogenic diets and caloric restriction, although these have not yet been well studied in patients with AD (Wilkins, 2016). Some clinical evidence provides a rationale for the use of mitochondrial nutrients, such as a meta-analysis of 21 double-blind clinical trials on acetyl-L-carnitine in patients with mild cognitive impairment and AD showing modest but significant efficacy on cognitive function, mood and brain bioenergetics (Montgomery, 2003). Similarly, preliminary clinical trials on nicotinamide adenine dinucleotide (NADH), a coenzyme in cellular energy metabolism, suggest it may stabilize disease progression and improve cognitive function in patients with AD (Birkmayer, 1996, Demarin, 2014, Prousky, 2011).

Targeting Brain Insulin Signaling

Insulin resistance and hyperglycemia have been suggested to play a causal role in the development of AD, although the exact mechanisms are not fully understood these phenomena can contribute to neuronal death followed by neurodegenerative diseases (Pardeshi, 2017). Importantly, pronounced brain insulin resistance in AD occurs independently of peripheral insulin resistance such as in type 2 diabetes mellitus (Talbot, 2012). Although conventional hypoglycemic drugs do not reduce AD risk in newly diagnosed diabetics, there are lines of evidence that suggest improving insulin sensitivity may still be a valuable strategy (Huang, 2014).
Magnetic resonance imaging and biomarker studies have revealed associations between intake of dietary sugars and sugar-sweetened beverages and pre-clinical AD (Berti, 2015, Pase, 2017). And a population-based study in elderly persons found that higher caloric intake from carbohydrates increased risk of cognitive impairment or dementia. Because chronic excess of refined carbohydrates and sugars may contribute to cognitive deficits a low carbohydrate diet, which is superior to drug therapy for optimizing insulin sensitivity and blood glucose, should be considered (Roberts, 2012, Stefanidis, 2012). Nutritional insulin sensitizing agents may be a useful addition to dietary therapy. Resveratrol appears to be particularly promising as it has well documented hypoglycemic effects as well as evidence from preliminary human clinical trials to suggest it may modify AD pathology, improve brain function and attenuate cognitive decline (Szkudelski, 2015, turner, 2015, Moussa, 2017, Köbe 2017).

Multi-Targeted Nutritional Approaches

Combined nutritional therapies may have advantages over traditional single-compound approaches in that they have multi-targeted effects that influence the wide-spread pathology of AD, as opposed to the limited actions of traditional monotherapeutic approaches. Some clinical evidence supports the use of nutrient cocktails, in particular a combination of folic acid (400 mcg), vitamin B12 (6 mcg), alpha-tocopherol (30 IU), S-adenosyl methionine (400 mg), n-acetylcysteine (600 mg), and acetyl-L-carnitine (500 mg) improved cognitive performance and mood in individuals with AD versus placebo over treatment periods ranging from 9 months to 2.4 years (Chan, 2008, Remington, 2015, Remington, 2016). And a clinical trial of a supplement containing Bacopa monnieri extract (100 mg), microalgae (74 mg), astaxanthin (2 mg), phosphatidylserine (30 mg), and vitamin E (30 mg) reported improved memory skills in old age subjects suffering from mild cognitive impairment after 60 days of treatment (Zanotta, 2014). The effects of different combination formulas may not be generalizable to other nutrient combinations, however, as one study suggested that a unique combination of α-tocopherol (800 IU), vitamin C (500 mg), alpha lipoic acid (900 mg) may have worsened cognitive decline (Galasko, 2012).

Personalized B Vitamin Therapy

In patients with mild cognitive impairment or AD and coexistent low B vitamin status and/ or high blood homocysteine, B vitamin supplementation has been shown to reduce atrophy of brain regions involved in the AD process and slow of cognitive decline (Smith, 2016). Elderly subjects with mild cognitive impairment and elevated homocysteine who were treated with B vitamins (folic acid 0.8 mg, vitamin B6 20 mg, vitamin B12 0.5 mg) over a 2.5 year period were found to have significantly reduced shrinkage of the whole brain volume (Douaud, 2013), and cognitive decline over a treatment period of 2.5 years. In middle-aged and elderly patients with high blood homocysteine (folic acid 0.8 mg, vitamin B6 10 mg, vitamin B12 0.25 mg) was found to improve cognitive function within 14-weeks, suggesting clinical effects may be relatively quick (de Jager, 2012). Importantly, baseline omega-3-fatty acid status was found to have a strong influence on the effect of B vitamin therapy with omega-3 fatty acid levels in the upper range of normal critical for slowing brain atrophy (Oulhaj, 2016).

Individual B vitamins have also been found to have important clinical and disease modifying effects. In older age people with low background dietary folic acid exposure and mild cognitive impairment or newly diagnosed with AD, folic acid supplementation (400 µg/day) was shown to improve cognitive function, and biomarkers such as homocysteine and the inflammatory cytokine TNF-α over 6-12 months (Ma, 2016, Chen, 2016).

Vitamin B12 deficiency is a risk factor for dementia and treatment of deficiency may improve cognitive dysfunction by impacting the underlying disease pathophysiology (Werder, 2010). In patients with dementia and B12 deficiency, supplementation has been shown to improve neuropsychological function (Eastly, 2000), and reduce delirium (Kwok, 2008). Although not all studies have reported benefits (van Dyck, 2009). Studies of B12 treatment in AD are needed to clarify its influence on the pathology and clinical outcomes.
Betaine has been proposed as a treatment for patients with AD and methylenetetrahydrofolate reductase (MTHFR) genotype mutations, as it may be superior to folate and vitamin B12 for homocysteine lowering (Chai, 2013). In a clinical study, AD patients were treated with betaine (50, 100, or 200 µg/kg) for 1 month, after which time there was a significant reduction in homocysteine, inflammatory markers, and improvements in cognitive function when compared to controls (Sun, 2016).

Optimizing Omega-3 Fatty Acid Status

Higher dietary intake of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) from fish have been associated with lower risk of dementia and Alzheimer’s disease (Wu, 2015). And higher red blood cell DHA/EPA levels have been associated with a lower risk of dementia, and larger total brain and hippocampal volume (Pottala, 2014). Over 20 clinical trials have assessed the effects of DHA and EPA alone or with other nutrients in AD, but have produces mixed therapeutic results (Fraga, 2017). *The O megAD* (Omega-3 and Alzheimer’s Disease) was designed to clarify the role of EPA/ DHA supplementation in AD, and has demonstrated that supplementation with DHA (1.7 g) and EPA (0.6 g) over 6-months increased omega-3 levels in cerebrospinal fluid (Freund Levi, 2014), preserved cognitive function (Eriksdotter, 2015), and influenced expression of genes involved in inflammation regulation and neurodegeneration. Increasing dietary intake of DHA/ EPA or supplementation has a strong theoretical basis, modifies the disease process, and may reduce cognitive decline. *ApoE4* allele-positive patients may be more susceptible to dietary deficiency in omega-3 fatty acids (Nock, 2017).

Lipoic Acid as a Disease Modifying Agent

Lipoic acid has several actions that may modify AD pathology, including improving mitochondrial function, increases acetylcholine production, chelating redox-active metals, increasing the levels of reduced glutathione and decreasing inflammation (Holmquist, 2007). A clinical study of lipoic acid (600 mg/day) in AD patients found that treatment significant slowed in cognitive decline at 8- and 16-month follow-up (Fava, 2013). Subsequently, a combination of omega-3 fatty acids (675 mg DHA and 975 mg EPA) plus alpha lipoic acid (600 mg) was found to slow cognitive and functional decline in AD patients over 12-months (Shinto, 2014).

Improving Brain Phospholipid Supply

Phosphatidylserine (PS) is a major phospholipid in the brain and a candidate therapy for dementia treatment and prevention (Pepeu, 1996). Several studies have suggested that supplementing with PS can improve cognitive health, particularly in the elderly. In a pilot study, PS supplementation (300 mg/ daily) for 12 weeks significantly improved memory and mental flexibility (Richter, 2013). And elderly subjects with memory complaints given a PS containing omega-3 supplement (300 mg PS and 37.5 mg EPA/ DHA daily) for 6 weeks experienced a 42% increase in memory recall (Richter, 2010). In subjects with Alzheimer’s disease, PS and phosphatidic acid (300 mg PS + 240 mg PA/day) for 2 months stabilized daily functioning and emotional state (Moré, 2014). And in a 6-month study, PS (300mg or 100 mg/ daily) significantly improved memory function elderly subjects with memory complaints at both dosages (Kato-Kataoka, 2010).

Replenishing Brain Glutathione with N-acetylcysteine

N-acetylcysteine (NAC) is a glutathione precursor with potent antioxidant, pro-neurogenesis and anti-inflammatory properties that suggest a potential therapeutic role in AD (Skvarc, 2017). The ability of NAC to elevate glutathione (GSH) in the brain is of particular importance as GSH has several neuroprotective effects and reduces elevated oxidative stress, a characteristic feature of the AD brain (Pocernich, 2012). Clinical studies of NAC in AD have suggested it can improve cognitive function as a monotherapy (Adir, 2001), or as a combination therapy with other nutrients (Chan, 2008, Remington, 2015, Remington, 2016).
Discussion

Although the term ‘orthomolecular psychiatry’ was defined over 60-years ago, it is evident that a considerable body of emerging science in recent years builds a strong-evidence base for its applicability to AD today. Research supporting the practice of orthomolecular psychiatry can be immediately translated applied in a clinical setting as a personalized nutritional approach that considers the unique genetic susceptibilities, biochemistry and nutritional status and requirements of the patient. In this context, orthomolecular medicine has the potential to prevent cognitive decline and preserve or improve cognitive function by modifying the underlying disease pathology.

It is important to highlight that the research summarized here demonstrates several important examples of the concept of ‘biochemical individuality,’ one of the foundational concepts of orthomolecular medicine (Williams, 1956). With the significance of individual variability in physiology and biochemistry in mind, specific nutritional interventions should be targeted to those most likely to benefit, such as people with low dietary intake, genetic factors that increase requirement, biochemical evidence of deficiency, or pathophysiology that increases functional requirements. Indiscriminate use of nutrients, in some cases, was not found to be effective while, in contrast, nutritional therapies that target genetic, biochemical or environmental individuality may be more successful.

Against the backdrop of failed drug therapy for AD, nutritional therapy shows tremendous promise for disease treatment. The lack of patentability, wide availability and relatively low cost of nutritional therapies should be incentives for further research, not a hindrance. It is also important to emphasize the excellent safety profile of nutritional treatments when compared to drug therapies. More research is needed to support the practice of orthomolecular psychiatry in AD, but while we wait we already have orthomolecular medicine, an established conceptual and practical model for the management of neurodegenerative disease and optimization of brain health in a clinical setting.

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