Efficacy of three nonpharmacological interventions for Alzheimer's disease

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EFFICACY OF THREE NONPHARMACOLOGICAL INTERVENTIONS FOR ALZHEIMER’S DISEASE

by

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I would like to thank all of the scientists studying this disease. Without your curiosity and knowledge, this thesis would have been impossible. Finally, to all the people suffering with or caring for people with Alzheimer’s disease, never give up hope. We will find a cure.
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AARON ARTILES

ABSTRACT

The leading cause of dementia globally is Alzheimer’s disease, and its incidence is increasing. Besides the immense clinical impact on the afflicted patient, Alzheimer’s disease has a significant social impact on the patient’s family and friends.

Pharmacological interventions have shown modest results and are lacking in successful disease-modifying therapies. Three of the most common nonpharmacological interventions for Alzheimer’s disease are cognitive, exercise, and nutritional methods. The goal of this study was to analyze the efficacy of these interventions in an effort to uncover the most promising nonpharmacological strategies with which to utilize moving forward.

This thesis reviewed a large number of studies evaluating different cognitive, exercise, and nutritional interventions for patients suffering from Alzheimer’s disease. The review considered each study by looking at both the methods used and the results obtained. The cognitive intervention studies revealed modest results, with cognitive rehabilitation being the most promising cognitive intervention. Exercise interventions showed positive results for the patients’ activities of daily living and quality of life. Although nutritional interventions produced modest improvements, the Mediterranean diet had the most encouraging results.
Based on the analysis of these studies, this thesis concludes that cognitive rehabilitation, exercise, and the Mediterranean diet are the most effective nonpharmacological interventions for managing patients with Alzheimer’s disease in the future.
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LIST OF ABBREVIATIONS

Aβ .................................................................................................. Amyloid-beta
AD .................................................................................................. Alzheimer’s disease
ADAS-cog..........................Cognitive portion of the Alzheimer’s disease Assessment Scale
ADL ...........................................................Activities of daily living
APP ...........................................................Amyloid precursor protein
CIBIC-plus..........................Clinician’s Interview-Based Impression of Change Scale
CMI ...........................................................Cognitive motor intervention
CNS ...........................................................Central nervous system
CR ...........................................................Cognitive rehabilitation
CS ...........................................................Cognitive stimulation
CT ...........................................................Cognitive training
DHA ...........................................................Docosahexaenoic acid
EPA ...........................................................Eicosapentaenoic acid
GDS ...........................................................Geriatric Depression Scale
HDRS ...........................................................Hamilton Depression Rating Scale
IADL ...........................................................Instrumental activities of daily living
MCI ...........................................................Mild cognitive impairment
MMSE ...........................................................Mini-Mental State Examination
MRI ...........................................................Magnetic resonance imaging
NFT ...........................................................Neurofibrillary tangle
NMDA ...........................................................N-methyl-D-aspartate
NT .................................................................No treatment
PUFA .............................................................Polyunsaturated fatty acid
RT ..............................................................Relaxation therapy
INTRODUCTION

Alzheimer’s Disease

Approximately 10% of people over 70 years of age have substantial loss of memory. In the majority of these cases, Alzheimer’s disease (AD) is the cause. It has been estimated that the total cost of providing care for a patient suffering from AD exceeds $50,000 without including the significant toll it takes on the people closest to the patient (Seeley & Miller, 2015). There is an excess of 35 million people who are suffering from dementia today. Projections indicate this number will increase to 70 million within 20 years. Dementia is the number one causative factor for the aging population to become disabled. In 2010, it was estimated the overall global cost of dementia exceeded $600 billion, and with the growing aging population, this number is only going to increase. However, the emergence of novel and less expensive treatments for Alzheimer’s disease and dementia may potentially decrease this cost (Wimo, Jönsson, Bond, Prince, & Winblad, 2013).

There are three main disease stages observed in patients with AD: early/mild, middle/moderate, and late/advanced (Seeley & Miller, 2015). Mild Cognitive Impairment (MCI) precedes early stage AD; however, approximately half of the patients with MCI eventually acquire AD. The natural progression of Alzheimer’s disease usually begins with a gradual decrease in episodic memory, which leads to dementia that slowly worsens while the disease takes its course. The first presentation of the disease is the insidious increase in forgetfulness and is classified as ‘early’ with a Mini-Mental
State Examination (MMSE) score of approximately 20-24 (“Tests for Alzheimer’s & Dementia,” n.d.). Occurrences of everyday life start to be forgotten and the names of people that are not well known become hard to remember for the patient. The patient may begin to lose objects, and occasionally scheduled appointments may be missed. Later on, the patient may ask the same question repeatedly, and he or she may forget conversations that just occurred or topics that were recently discussed (Ropper, Samuels, & Klein, 2014). To some extent, recent memories are forgotten whereas memories of the distant past are preserved; however, memory loss can extend to distant memories as well. As the disease progresses to moderate (MMSE score 13-20), it affects more than just the patient’s memory (“Tests for Alzheimer’s & Dementia,” n.d.). For example, speech is affected, and the afflicted patient begins to have slurred speech. This disability in speech also extends to writing, and the patient may begin to misspell words more often (Ropper et al., 2014). Normal activities, such as controlling finances, navigation, following instructions, and household chores, are often impaired. However, activities that follow a routine as well as superficial social interactions can be maintained even as the disease becomes more severe (Seeley & Miller, 2015).

After years of decline, the patient’s language skills begin to deteriorate significantly, and he or she may no longer be able to speak in complete sentences or much at all. This is the advanced stage (MMSE less than 12) (“Tests for Alzheimer’s & Dementia,” n.d.). Similar to speaking and reading skills, arithmetic abilities deteriorate (Ropper et al., 2014). As the disease continues to progress, it is likely that the patient’s personality is altered, and the patient may become either more sedentary or overactive.
About 30% of patients with AD develop depression during the course of the disease. As AD proceeds, patients may develop incontinence and become much more reliant on others to perform activities of daily living (ADL) (Carlsson, Gleason, Puglielli, & Asthana, 2009). The most routine and automatic movements are the only actions that the patient maintains (Ropper et al., 2014). The most common causes of death for patients in the last stages of AD are aspiration pneumonia, dehydration, malnutrition, pulmonary embolism, heart disease, or a secondary infection. The typical duration from the onset of AD to death is usually eight to ten years, but the time can be significantly shorter or longer (Seeley & Miller, 2015).

During the late stages of AD, the brain atrophies to a weight that is approximately 80% of what it used to be. The atrophy is most prominent in the frontal and temporal lobes of the brain, but other areas can atrophy as well (Ropper et al., 2014). The pathology of AD is characterized by the presence of neuritic plaques and neurofibrillary tangles (Figure 1). These plaques are caused by the accumulation of amyloid-beta (Aβ) peptide, whereas the neurofibrillary tangles are the result of hyperphosphorylated tau protein that accumulates inside neurons (De-Paula, Radanovic, Diniz, & Forlenza, 2012).
Figure 1. Pathology of Alzheimer’s disease. This slide shows a sample of cortex taken from the brain of a patient with AD. The three arrowheads (A) point to a neuritic plaque showing extracellular deposits of Aβ peptide. Arrow B points to a neuron containing neurofibrillary tangles. (Figure taken from Carlsson et al., 2009).

Amyloid precursor protein (APP) is the protein responsible for the formation of Aβ peptide in brain tissue. APP is a transmembrane protein that is largely expressed throughout the central nervous system (CNS) (De-Paula et al., 2012). Aβ peptide ranges in size from 39 to 42 amino acids in length (Seeley & Miller, 2015). The Aβ peptides with lengths of 40 and 42 amino acids, Aβ_{40} and Aβ_{42}, respectively, are the most common
Aβ peptides found in the brain. Aβ42 is the peptide that is most prone to aggregation in the brain tissue to form neuritic plaques. Therefore, this peptide is the most important in understanding the pathogenesis of AD (De-Paula et al., 2012).

The transmembrane protein APP is cleaved in two distinct pathways (Figure 2). The first pathway is the secretory pathway, which is normal and does not cause the aggregation of Aβ peptide. In this non-amyloidogenic pathway, the APP protein is cleaved in sequence by α-secretase and then by γ-secretase (De-Paula et al., 2012). The α-secretase cleaves APP inside the region that makes up the Aβ peptide; therefore, the Aβ peptide cannot be formed (Braak & Braak, 1998). If the APP protein is instead cleaved by β-secretase and then γ-secretase before it can be cleaved by α-secretase, Aβ40 and Aβ42 peptides can be released into the extracellular fluid (Selkoe, 2011). Although the Aβ peptide is secreted from the cell as a monomer, in the disease state the protein aggregates with other monomers to form oligomers (De-Paula et al., 2012).
Figure 2. Cleavage of APP by α-, β-, and γ-secretase. In the first step, APP can be cleaved by either α-secretase or β-secretase. If APP is cleaved by α-secretase and then by γ-secretase, a nontoxic product (P3) is formed. However, if APP is cleaved by β-secretase followed by γ-secretase, the toxic Aβ42 can be formed, potentially contributing to the formation of neuritic plaques. (Figure amended from Seeley & Miller, 2015)

The second type of pathological lesion found in AD is the neurofibrillary tangle (NFT) (Figure 1, Arrow B). These lesions occur independently from the neuritic plaques that are caused by Aβ42 in patients with AD (Selkoe, 2011). NFTs are found in the cytosol of neurons rather than in the extracellular matrix where amyloid plaques occur (Carlsson et al., 2009). When the tau protein becomes abnormally phosphorylated, it can no longer perform its normal function of stabilizing microtubules for neuronal transport down the axon (Figure 3). Because tau no longer stabilizes the microtubules, neuronal
transport is affected, and NFTs can be found in the cytoplasm as a result of the accumulation of phosphorylated tau (Seeley & Miller, 2015). NFTs are seen as paired filaments, and the aggregates have ubiquitin incorporated into them. Ubiquitination may be an attempt by the neuron to take care of the NFTs through proteolysis; however, this process is not successful. Eventually, the accumulation of NFTs causes the neuron to lose its function, resulting in the death of the cell (Selkoe, 2011).

![Figure 3. Neurofibrillary tangle formation.](image)

The protein tau helps to stabilize microtubules within the cytosol (left). When tau becomes hyperphosphorylated, it is no longer able to perform this function. The microtubule becomes destabilized, and tau aggregates into paired filaments (right). (Figure taken from Selkoe, 2011)
Pharmacological Treatment for Alzheimer’s Disease

A failure in the brain’s cholinergic system has long been suggested as one of the causes of AD (Hogan, 2014). The efficacy of cholinesterase inhibitors to treat the symptoms of Alzheimer’s disease has been well documented within the literature (Borisovskaya, Pascualy, & Borson, 2014). The three most widely administered cholinesterase inhibitors are donepezil, galantamine, and rivastigmine (Jellinger, 2007). These three drugs exhibit a clinically significant effect on the symptoms of the disease without having an effect on the underlying pathogenesis (Jellinger, 2007). For example, in the two-year study on galantamine by Hager et al. (2014), a lower mortality rate was observed in the group administered galantamine compared to the placebo group. Also, the patients treated with galantamine showed less cognitive deterioration, as described by mean Mini-Mental State Examination (MMSE) scores (Figure 4), and an increase in activities of daily living (Hager et al., 2014). Similarly, in the study performed by Richarz, Gaudig, Rettig, and Schauble (2014), a cognitive benefit to galantamine treatment was observed in patients with mild to moderate Alzheimer’s disease.
Figure 4. Mean change in Mini-Mental State Examination scores over time. The group administered galantamine shows an initial increase in MMSE scores after the first six months. Significant differences are seen between the two control and AD groups in MMSE scores for all time points after baseline. SE = standard error. (Figure taken from Hager et al., 2014)

There have been concerns raised about possible adverse effects of cholinesterase inhibitors, including bradycardia, syncope, bronchoconstriction, and weight loss (Hogan, 2014). Borisovskaya et al. (2014) reported gastrointestinal consequences such as vomiting, nausea, and diarrhea as likely adverse effects of cholinesterase inhibitors.

In more severe stages of AD, memantine in combination with cholinesterase inhibitors has been shown to be effective (Jellinger, 2007). Unlike cholinesterase
inhibitors which affect the cholinergic system of the brain, memantine affects the glutaminergic system (Borisovskaya et al., 2014). Memantine is an antagonist of the N-methyl-D-aspartate (NMDA) receptor (Waite, 2015). In the study by Dysken et al. (2014), memantine was shown to have no effect in patients with mild to moderate AD compared with the study’s placebo group. On the other hand, in patients with moderate to severe AD, a significant benefit of memantine was documented, showing improvements in ADL, cognition, and behavior (Waite, 2015). Nevertheless, it has been argued that the economic cost of memantine is not worth the meager benefit of the drug for patients with AD (Waite, 2015). Cholinesterase inhibitors and memantine are the only major pharmacological treatment options for patients with AD. These interventions, however, only treat the symptoms of the disease and do not alter the disease-causing lesions (Chu, 2012). Pharmacological interventions for this purpose are currently in clinical trials (Chu, 2012).

More recently, novel anti-amyloid immunotherapy strategies have been developed. The study by Schenk et al. in 1999 was the first study using a transgenic animal model to show that through immunization with Aβ42 there was a significant reduction or absence of amyloid plaques. With the use of mouse models, this study was able to demonstrate a possible benefit to anti-amyloid immunotherapy (Schenk et al., 1999). This strategy, called passive immunotherapy, used monoclonal antibodies to target Aβ peptide in the hope to inhibit Aβ peptide aggregation and increase peptide removal. Passive immunotherapy remains to be the most effective disease-modifying intervention for AD (Rafii & Aisen, 2015).
There have been other trials using different monoclonal antibodies targeting Aβ peptide with varying degrees of success. In the 2014 phase III clinical trials by Doody et al., there was a trend that solanezumab, a monoclonal antibody, caused an increase in cognition in patients with mild AD in one of the two trials. This finding, however, lacked statistical significance. When patients in both trials were pooled together, the benefit of solanezumab was significant (Doody et al., 2014). In a clinical trial with crenezumab, another monoclonal antibody, there was a trend that the drug showed a slowing of cognitive decline in patients with mild AD (Rafii & Aisen, 2015). Finally, gantenerumab is another monoclonal antibody that binds to Aβ peptide with high affinity (Bohrmann et al., 2012). In a phase II clinical trial of gantenerumab started in 2012, the testing was ceased in 2014 because of the lack of efficacy of the drug (Rafii & Aisen, 2015).

**Specific Aims and Objectives**

Because of the economic and social costs of treating AD using pharmacological methods, as well as the modest benefit gained from these interventions, it is imperative to examine other treatment options for patients with AD. Therefore, this thesis will explore the efficacy of three nonpharmacological approaches to treat patients with AD: cognitive, exercise, and nutritional interventions.

The aims of this thesis are:

1. Analyze separately the efficacy of three nonpharmacological interventions for AD: cognitive, exercise, and nutritional interventions.
2. Based on the literature, decide if there is significant evidence of positive effects with these nonpharmacological interventions.

3. Analyze the practicality of using any of the three nonpharmacological interventions to treat patients with AD.

4. Propose future directions using one or more nonpharmacological interventions for AD.
PUBLISHED STUDIES

The many studies performed on the pharmacological interventions for AD show a reduction of symptoms; however, these positive results are modest (Olazarán et al., 2010). There are a number of pharmacological agents that have been targeted to reverse or slow the deterioration in AD, including donepezil, huperzine A, and cholinesterase inhibitors (Rodakowski, Saghafi, Butters, & Skidmore, 2015). These treatments have not been able to correct the long-term result of cognitive decline characteristic of AD (Rodakowski et al., 2015).

Therefore, there is a need for studies assessing nonpharmacological interventions as an alternative approach. In addition, because of the current economic and societal cost of AD, the need for nonpharmacological interventions has become critical (Olazarán et al., 2010). There are a number of benefits from using nonpharmacological interventions rather than the current pharmacological approaches to treat AD. In particular, there are limited adverse side-effects from these interventions as opposed to those seen in pharmacological treatments (Rodakowski et al., 2015). Cholinesterase inhibitors, for example, show side-effects including bradycardia, syncope, bronchoconstriction, and weight loss (Hogan, 2014).

Three of the most widely studied nonpharmacological interventions for Alzheimer’s disease are cognitive, exercise, and nutritional interventions.
Cognitive Interventions for Patients with Alzheimer’s Disease

For the past 30 years, there has been more research evaluating cognitive intervention techniques for the treatment of patients with AD. Cognitive interventions typically involve training to improve cognitive abilities and function. The end goal of this intervention is to delay or prevent the cognitive decline characteristic of AD (Acevedo & Loewenstein, 2007). There are three types of cognitive interventions that are generally found in the literature: cognitive training (CT), cognitive stimulation (CS), and cognitive rehabilitation (CR) (Borisovskaya et al., 2014). The three treatment strategies are described in Table 1.

Table 1. Types of cognitive intervention. Abbreviations – ADL: activities of daily living and IADL – instrumental activities of daily living (Table taken from Borisovskaya et al., 2014)

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<th>Definition of the cognitive intervention</th>
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<td>Cognitive training (CT)</td>
<td>Practice on a set of standard tasks to increase particular cognitive function, meant to support accomplishment of ADL/IADL</td>
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<td>Cognitive rehabilitation (CR)</td>
<td>Individualized treatment; therapist works with the patient and family to devise strategies to identify and address personally relevant goals, with less emphasis on particular cognitive functions</td>
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<tr>
<td>Cognitive stimulation (CS)</td>
<td>Engagement in a range of activities designed to enhance general cognitive and social functioning, administered in a group setting</td>
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In the randomized control trial by Davis, Massman, and Doody in 2001, a combination of different cognitive interventions were tested and compared to a control group. The study used 27 patients diagnosed with probable AD. The cognitive intervention consisted of face-name training, spaced retrieval, and cognitive stimulation. These strategies were the most promising cognitive interventions at the time. Spaced retrieval is a cognitive intervention performed by asking the patient to recall something over increasingly longer and longer periods of time. This method had previously been found to increase the patient’s memory of objects. The placebo group went through intervention consisting of conversation, videotapes, and studying previously learned material (Davis et al., 2001).

This study by Davis et al. (2001) showed some differences between the experimental and control groups; however, the results did not strongly support the hypothesis that patients might show improved overall recall as well as neuropsychological functioning and quality of life. Although the experimental group exhibited improved recall, Davis noted that the intervention did not produce any beneficial effects in the experimental group relating to depression, motor speed, visual or verbal memory, word generation, dementia severity, or patient quality of life. Furthermore, there was no change in Mini-Mental State Examination (MMSE) scores (Davis et al., 2001). The MMSE assesses 20 different areas of cognitive functioning, such as language, attention, and visuospatial skills (Small, Viitanen, & Bäckman, 1997).

In the study by Cahn-Weiner, Malloy, Rebok, and Ott in 2003, similar results were reported. The researchers noted that there may be beneficial effects to using
cholinesterase inhibitors in combination with a cognitive training intervention. Therefore, 34 patients with probable AD, who were also taking cholinesterase inhibitors, were assigned to a cognitive training group or a control group. The purpose of the study was to measure the neuropsychological condition of the patients before and after the intervention as well as ADL and memory assessed by caregivers. The experimental group went through a six-week memory-training program consisting of categorization and visualization. The control group participated in a six-week intervention consisting of discussions without memory-training exercises (Cahn-Weiner et al., 2003).

The results of the Cahn-Weiner et al. (2003) study were very similar to the results of the Davis et al. (2001) study. No neuropsychological, ADL, or “everyday memory function” benefits were found during the study (Cahn-Weiner et al., 2003). The only improvement was in the patient’s ability to recall words from the word lists used during the tests (Cahn-Weiner et al., 2003). This was similar to the findings of Davis and his colleagues (Davis et al., 2001) who found that there was a significant difference in the patient’s ability to recall information before and after the cognitive intervention.

Next, the study by Olazarán et al. in 2004 set out to investigate the effects of a cognitive motor intervention (CMI) that consisted of “cognitive exercises, plus social and psychomotor activities.” The experimental group receiving the CMI was tested against the control group receiving psychosocial support without the cognitive interventions. Seventy-five patients taking cholinesterase inhibitors with mild cognitive impairment (MCI) or probable AD were divided into two groups, 38 in the control group and 37 in the experimental group (Olazarán et al., 2004).
This study by Olazaran et al. (2004) assessed the benefits of CMI by looking at the changes in the cognitive subscale of the AD Assessment Scale (ADAS-cog) as well as MMSE, ADL using a questionnaire, and geriatric depression using the Geriatric Depression Scale (GDS). ADAS-cog measures “memory, language, ideational praxis, and visuospatial ability.” Patients in the experimental group were able to maintain their ADAS-cog measure through the first 6 months of treatment, whereas the control group showed deterioration in this category. In addition, at 12 months the experimental group exhibited a beneficial increase in their GDS scores. Furthermore, the results of the study indicated a trend that MMSE scores and ADL scores in the experimental group did not deteriorate as dramatically over the course of the year as they did in the control group. The results showed some evidence of a possible beneficial effect of cognitive interventions on mood and cognition (Olazarán et al., 2004).

The 2004 trial by Loewenstein, Acevedo, Czaja, and Duara was an attempt at combining multiple cognitive intervention strategies into one training program. Twenty-five patients received cognitive training that consisted of face-name associations, time and place orientation, procedural and motor memory exercises, exercises in maintaining attention, and training in useful functional skills like making change and paying bills. The 19 patients in the control group went through “mental stimulation training” during which they played computer games with memory exercises and word games. As in the studies previously discussed, all of the participants were taking cholinesterase inhibitors at the time of the study (Loewenstein et al., 2004).
The results of the Loewenstein et al. (2004) study showed some beneficial results from the cognitive training intervention in comparison with the mental stimulation control group. These results, including better face-name associations, orientation, and functional skills, suggested that cognitive interventions could have beneficial effects on real-world tasks, possibly improving quality of life and ADL (Loewenstein et al., 2004).

In the 2010 study by Niu, Tan, Guan, Zhang, and Wang, the effect of a cognitive stimulation (CS) therapy was tested. Thirty-two patients with probable AD were enrolled in the study with 16 patients in the experimental cognitive stimulation group and 16 patients in the control group. All of the participants in the study were taking cholinesterase inhibitors before and during the study. The cognitive stimulation consisted of specific tasks exercising the patient’s executive functioning and working memory. The control group underwent a placebo therapy consisting of “communication exercises.” According to the results, the experimental group receiving cognitive stimulation showed improved neuropsychiatric symptoms, whereas the group receiving the placebo treatment showed a decline. Similarly, the MMSE scores of the cognitive stimulation group increased, whereas the scores of the placebo group decreased. The results of this study indicated that cognitive stimulation therapy could improve cognition, apathy, and depression in AD patients taking cholinesterase inhibitors (Niu et al., 2010).

The 2010 study by Clare et al. designed to study the effects of a cognitive rehabilitation (CR) program was completed. Unlike cognitive stimulation or cognitive training, cognitive rehabilitation takes an individualized approach. In order to do this, patients and families work with healthcare providers to devise a cognitive intervention
based on each patient’s needs and goals. Clare and her colleagues argued that CR was a better approach than other more standardized cognitive interventions because every patient has different requirements that need to be addressed. In this study, the researchers compared CR with a relaxation therapy (RT) group and a no-treatment (NT) control group. The study involved 69 patients who were diagnosed with AD and prescribed cholinesterase inhibitors. Each patient in the CR group focused on one or two goals during the intervention and was told to keep working on goals outside of the eight one-hour sessions (Clare et al., 2010).

The results of the Clare et al. (2010) study showed beneficial results for cognitive rehabilitation. For example, patient scores for goal performance and satisfaction improved after the CR intervention compared with the relaxation therapy and no-treatment groups. Also at the follow-up six months after the conclusion of the study, patients in the CR group rated their memory performance higher than the patients in the no-treatment group. Although the beneficial findings in this study were significant, it was difficult to determine whether they were clinically relevant (Clare et al., 2010).

The 2015 study by Kim also set out to study a cognitive rehabilitation (CR) intervention. Similar to the study by Clare et al. (2010), this cognitive intervention was individualized to each patient and was goal-oriented (Kim, 2015). However, Kim’s study was different from that of Clare et al. (2010) in that it incorporated cognitive training techniques into the cognitive rehabilitation intervention (Kim, 2015). The goal of the study was to see if CR in combination with some aspects of CT could improve the daily lives of patients with AD. To do this, 43 patients diagnosed with AD were assigned
randomly to a CR group and a control group. All patients participated in eight hour-long
sessions of either CR or a control therapy depending on their group. The CR was
centered on a personal goal of the patient and also included some cognitive training
exercises (Kim, 2015).

The results of the study by Kim (2015) were very similar to the results found by
Clare et al. (2010). Improvements were observed in patient performance and satisfaction
in the CR group. In addition, the CR group showed improvements in performance,
quality of life, and the orientation subscale of the MMSE. No improvements were
observed in the control group post-intervention. The results of this study indicated that
CR could benefit patients with early-stage AD and that it could be effective in helping
these patients with real-life activities (Kim, 2015).

**Exercise Interventions for Patients with Alzheimer’s Disease**

It has become apparent that physical exercise is necessary for brain health,
especially in the elderly. Exercise-induced beneficial changes in the brain with respect to
memory, executive functioning, and attention have been well documented in the literature
(Kirk-Sanchez & McGough, 2014). It has also been found that physical exercise can
have a protective effect against cognitive decline and can reduce the risk of cognitive
impairment (Ahlskog, Geda, Graff-Radford, & Petersen, 2011). Furthermore, it has been
reported that maintaining an exercise program can reduce mortality and extend the lives
of patients with AD. This trend is visualized in the survival curves obtained by
Scarmeas et al. (2011) (Figure 5).
Figure 5: Activity level survival curves. These curves show mortality rates of a cohort of patients with Alzheimer’s disease following three different levels of physical activity. (Figure taken from Scarmeas et al., 2011)

The study by Cot, Dawson, Sidani, and Wells in 2002 examined the possible beneficial effects of a walking and talking intervention for the treatment of patients with AD in a nursing home. These participants were divided into three groups: a “walk-and-talk group,” a “talk-only group,” and a group that received no intervention. Participants who were assigned to the walking and talking group received a 16-week intervention
where they walked and talked for 30 minutes, five times every week. Participants assigned to the “talk-only group” conversed with one other person for 30 minutes, five times each week for 16 weeks. Finally, the control group received no intervention. A total of 90 nursing home residents were used in this study with 30 AD patients in each of the groups. The purpose of this study was to find a possible beneficial effect of the walking and talking intervention on the resident’s level of function, ability to communicate, and ability to ambulate (Cott et al., 2002).

The results of the Cott et al. (2002) study showed no benefits for the patients assigned to the walking and talking intervention. In fact, there were no significant differences found between any of the three groups after the completion of the intervention. The outcome of this study indicated that there was no effect of the intervention on the patient’s ability to communicate, ability to ambulate, or functional status. Cot and colleagues argued that this result may be due to the fact that the AD patients enrolled in the study were at an advanced stage of the disease. Previous studies had found beneficial effects for AD patients that were less impaired with respect to ambulation and communication abilities (Cott et al., 2002).

The study by Rolland et al. in 2007 similarly used nursing home patients to test an exercise intervention. The exercise intervention involved walking, strength training, balance training, and flexibility training. The intervention lasted a total of 12 months and consisted of one-hour sessions, two times a week. A total of 134 patients with AD were separated into two groups, with one receiving the exercise intervention and the other receiving routine medical care. Participants’ activities of daily living performance,
physical performance, nutrition, behavioral disturbances, and depression were assessed. Normally, AD causes a decline in a patient’s capacity to perform activities of daily living. Therefore, an intervention that slowed this decline could prove clinically relevant. In addition, nursing home residents are often more inactive than patients outside of a nursing home, so an exercise program might be even more important for them (Rolland et al., 2007).

Although there was a decline in the ability to perform ADLs over the 12-month study period for patients in both the experimental and control groups, the AD patients in the experimental group declined only one-third as much as the patients in the control group (Rolland et al., 2007). Furthermore, Rolland and colleagues observed a significant correlation between the number of exercise sessions completed and deterioration in the capacity to perform ADLs (Figure 6). In addition, there was a significant improvement in walking speed for the experimental group at both 6 months and 12 months after the start of the intervention. However, there was no significant improvement in nutrition, depression, or behavioral disturbance (Rolland et al., 2007).
Figure 6. ADL and exercise adherence. This plot shows a significant Spearman correlation \((r)\) between more exercise sessions attended and less drastic decline in the capacity to perform activities of daily living (ADL). \(P = \) statistical significance. (Figure taken from Rolland et al., 2007)

Next, in the 2008 study by Miu, Szeto, and Mak, an exercise intervention was tested for patients with dementia in the hope of uncovering beneficial effects on physical function, cognition, and affect. The exercise intervention consisted of aerobic training on treadmill and bicycle, flexibility training, and ergometry. The exercise sessions lasted for one hour and occurred two times a week for 12 weeks. Of the 85 patients with dementia who participated in this study, 61% had AD, whereas the remaining 39% had other types of dementia. Thirty-six patients were assigned to the exercise intervention, and 49 patients were assigned to the control group that received routine medical treatment. Fifty-four of these patients were taking cholinesterase inhibitors. Patient assessments
occurred every 2 months for 12 months, and both cognitive and physical tests were given (Miu et al., 2008).

The results of the study by Miu and colleagues indicated that the exercise intervention had an effect on the physical function of the dementia patients but no effect on cognition (Miu et al., 2008). Although the exercise intervention only lasted for 12 weeks, the experimental group was able to maintain or improve in all physical assessments after 12 months, whereas the control group showed deterioration. Therefore, even though Miu’s study did not demonstrate that exercise affected cognition, it found that an exercise program could have an effect on ADL and physical function in patients with dementia, including patients with AD (Miu et al., 2008).

The pilot study in 2009 by Steinberg, Leoutsakos, Podewils, and Lyketsos evaluated another exercise intervention for patients with AD still living at home. Twenty-seven patients diagnosed with probable AD were assigned to either the exercise intervention group, consisting of aerobic exercise as well as strength training and balance and flexibility training, or the control group, receiving a home safety assessment. The main objective of Steinberg’s study was to assess the effects of exercise intervention on the participants’ physical functioning, but effects on cognition, neuropsychiatric symptoms, and quality of life also were evaluated. The study demonstrated trends indicating that the experimental group improved on a test for hand function, predictive of ability to perform ADLs, as well as a test for leg strength. No benefits of the exercise intervention were detected in cognition, neuropsychiatric symptoms, or quality of life (Steinberg et al., 2009).
In a study in 2011, Venturelli, Scarsini, and Schena tested an exercise intervention on patients with advanced stages of AD. All of the patients were currently living in a nursing home. The exercise intervention consisted of 30 minutes of walking, four times each week. Twenty-one patients were assigned to an exercise intervention group or a control group consisting of nursing home social activities (e.g., bingo and sewing). The walking intervention lasted 24 weeks, and patients were assessed at baseline and following the completion of the intervention. Patients were assessed on their ability to perform ADLs and physical functions, and global cognition. Venturelli and colleagues wanted to determine whether the walking intervention had a beneficial effect on the deterioration caused by late stage AD (Venturelli et al., 2011).

The results of Venturelli’s study showed positive results for the group receiving the exercise intervention (Venturelli et al., 2011). After the 24-week intervention, the experimental group showed a significant improvement in the distance they could walk in six minutes, whereas the control group showed a decline in their performance on this walking test. In addition, the experimental group demonstrated a significant improvement in their ability to perform ADLs, even though the control group neither improved nor declined. Finally, the experimental group was able to maintain its MMSE score after the 24-week intervention, whereas the control group showed a decline on this global cognition score (Venturelli et al., 2011).

The exercise program tested by Vreugdenhil, Cannell, Davies, and Razay in 2012 consisted of a daily exercise routine with 10 different exercises for lower and upper body strength and balance. These exercises were in addition to 30 minutes of brisk walking.
Forty patients living with AD were divided into two groups: one receiving this exercise intervention lasting for four months and one receiving routine medical care as control. Participants in the experimental group exercised daily. The purpose of Vreugdenhil’s study was to see if there was a beneficial effect of the exercise program on cognition, ability to perform ADLs, physical function, depression, global change in function, and caregiver burden (Vreugdenhil et al., 2012).

The results of the study by Vreugdenhil and his colleagues showed that when comparing them with the control group, the group receiving the exercise intervention improved in cognition, physical function, and ability to perform ADLs (Vreugdenhil et al., 2012). Moreover, a trend observed indicated improvement on the depression scale and assessment of caregiver burden. These results suggested that a daily exercise program could benefit cognition, physical function, and ability to perform ADLs in AD patients (Vreugdenhil et al., 2012).

Likewise, the 2015 pilot study by Holthoff et al. implemented an exercise program on AD patients living at home. Thirty patients participated in the study, all of whom were diagnosed with AD. All of the patients in the study were taking cholinesterase inhibitors, memantine, or both drugs. The exercise program consisted of physical activity using a bicycle ergometer and lasted for 12 weeks. The patients exercised three times each week for 30-minute sessions. Patients were assessed in physical functioning, ADL, clinical symptoms, and caregiver burden at 12 weeks when the study concluded and at 24 weeks for a follow-up assessment (Holthoff et al., 2015).
The results of Holthoff’s study (Figure 7) found that AD patients in the group receiving the exercise intervention showed initial improvements in their executive functioning, but after 24 weeks the patients were back to their baseline (Holthoff et al., 2015). This was in contrast to patients in the control group who showed a sustained decrease in their executive functioning over the entire 24 weeks. Physical functions improved for patients in the experimental group, whereas patients in the control group showed no improvement. Over the 24-week study, the control group displayed a decline in their ADL performance, behavior, depression, and anxiety, whereas the patients in the intervention group remained stable in these categories. There were no relevant effects of the exercise intervention on global cognition (Holthoff et al., 2015).
Figure 7. Effects of exercise intervention. Each line graph compares the results of the control group and the experimental group at the study’s three time points (0, 12, and 24 weeks). NPI = Neuropsychiatric Inventory. (Figure taken from Holthoff et al., 2015.)
Nutritional Interventions for Treatment of Patients with Alzheimer’s Disease

In recent years, it has become clear that nutrition has a significant effect on cognition as we age, and not receiving essential nutrients may increase the risk for developing AD (Mi, van Wijk, Cansev, Sijben, & Kamphuis, 2013). Having a balanced diet rich in nutrients required for neuronal health could have an effect on healthy aging and could reduce the risk of cognitive decline (Mi et al., 2013; Nelson & Tabet, 2015). The vast majority of the studies performed evaluating nutrition and AD have focused on the prevention of the disease and the effect of nutritional interventions on disease incidence. Most of these studies have used a healthy population and have studied the incidence of cognitive impairment (Nelson & Tabet, 2015). However, there have been a smaller number of randomized control trials on nutritional interventions for patients already diagnosed with AD. In this review of nutritional interventions for AD patients, the evidence is examined for interventions involving the Mediterranean diet, vitamins B12, B6, and folic acid, vitamin E, and omega-3 fatty acids.

Mediterranean Diet

The Mediterranean diet is composed of fruits and vegetables and other plant products, olive oil as a primary source of fat, fish, low levels of red meat and poultry, and a moderate consumption of wine (Frisardi et al., 2011; van de Rest, Berendsen, Haveman-Nies, & de Groot, 2015). This is the typical diet of the population living around the coast of the Mediterranean Sea (Frisardi et al., 2011). It was found that adhering to the Mediterranean diet could potentially be protective against developing AD.
(Scarmeas, Stern, Mayeux, & Luchsinger, 2006). In the 2006 study by Scarmeas and colleagues, the researchers found that patients who did not closely comply with the Mediterranean diet were more likely to acquire AD than those who were able to adhere to the diet.

There have been fewer studies on the effects of the Mediterranean diet on patients currently diagnosed with AD. However, there was one such study on this topic in 2007 by Scarmeas, Luchsinger, Mayeux, and Stern. In this study, 192 patients diagnosed with mild or moderate AD were assessed every one and a half years on how well they adhered to the Mediterranean diet. The patients were divided into three equal groups, or tertiles, depending on their adherence to the diet (high, middle, and low). Mortality was compared between these three groups (Figure 8). The results indicated that AD patients who were in the middle tertile of adherence lived an average of 1.33 years longer than patients in the low tertile, whereas patients in the high tertile lived an average of 3.91 years longer than patients in the low tertile (Scarmeas et al., 2007).
Figure 8. Mortality of Alzheimer’s disease patients and adherence to the Mediterranean diet. AD patients have a lower risk of mortality with a higher adherence to the Mediterranean diet. MeDi = Mediterranean diet. (Figure taken from Scarmeas et al., 2007)

Vitamins B12, B6, and Folic Acid

As observed in the literature, patients with AD tend to have lower levels of vitamin B12 and folate (Zheng et al., 2014). The plasma levels of the amino acid homocysteine are controlled by folate, vitamin B12, and vitamin B6 (Engelborghs, Gilles, Ivanoiu, & Vandewoude, 2014). Homocysteine has been found to be neurotoxic and is believed to be one of the causes of the symptoms in AD patients (Nelson & Tabet,
2015). The 2014 study by Zheng et al. with 116 participants, investigated the possibility that the behavioral symptoms observed in patients with AD may be due to high plasma levels of homocysteine. One group consisted of 40 patients diagnosed with AD who had behavioral and psychological symptoms. A second group consisted of 37 AD patients with no behavioral and psychological symptoms, and a third group consisted of 39 healthy individuals with neither AD nor behavioral and psychological symptoms. The plasma level of homocysteine was measured in each of the participants. Also, MMSE scores were recorded from each participant. Zheng and colleagues found that all of the participants in the AD group with behavioral and psychological symptoms had high levels of homocysteine, only some of the participants in the AD group with no symptoms had high levels of homocysteine, and none of the healthy group had high levels of homocysteine. Moreover, there was a negative relationship between plasma levels of homocysteine and MMSE score. This last finding indicated that levels of homocysteine had a direct correlation with cognitive decline in AD (Zheng et al., 2014). Although the study by Kim and Lee in 2014 supported the results of Zheng et al. (2014) that behavioral and psychological symptoms in AD were correlated with plasma homocysteine concentration, previous studies had found no correlation (Tabet, Rafi, Weaving, Lyons, & Iversen, 2006).

In order to regulate the elevated plasma levels of homocysteine, the effect of using supplements of B vitamins and folic acid, the synthetic form of folate, was studied in patients with mild cognitive impairment (MCI) and AD (Aisen et al., 2008; Kwok et al., 2011). The study by Kwok et al. (2011) investigated the effect of supplementation
with an oral dose of vitamin B12 and folic acid on cognitive impairment in patients with AD or vascular dementia. A total of 140 patients were divided into a group receiving the vitamin B12 and folic acid supplementation and a group receiving a placebo. During the 24-month study, global cognitive function and neuropsychiatric symptoms were assessed, and levels of homocysteine, vitamin B12, and folate were measured. Kwok and colleagues found that supplementation with vitamin B12 and folic acid was successful in increasing serum levels of vitamin B12 and folate and decreasing plasma levels of homocysteine. However, they were not able to show an effect on cognitive decline (Kwok et al., 2011).

The larger study, with 409 patients with AD, by Aisen et al. in 2008 found similar results. The experimental group received vitamins B6, B12, and folic acid, while the control group was given a placebo. The study measured the effects of the supplementation on the cognitive decline in AD patients. Although the intervention lowered the plasma levels of homocysteine, there was no beneficial effect on the course of the disease (Aisen et al., 2008).

Vitamin E

Free radicals are reactive molecules with an unpaired electron that are known to cause cellular damage and affect the normal functioning of cells (La Fata, Weber, & Mohajeri, 2014). Vitamin E acts as an antioxidant interacting with free radicals to prevent oxidative damage to molecules (Farina, Isaac, Clark, Rusted, & Tabet, 2012). Vitamin E is found in common foods such as nuts, oils, and fats (Farina et al., 2012). Although vitamin E is made up of a group of lipid-soluble molecules, α-tocopherol is the
form of vitamin E most commonly used as a supplement and most abundant in human cells (La Fata et al., 2014). Because the central nervous system is particularly susceptible to free radical damage which may contribute to AD, vitamin E has been an obvious candidate for AD interventions (Engelborghs et al., 2014).

The 2009 study by Lloret et al. investigated the effects of vitamin E supplementation in patients with AD. In this study, 57 patients received a dose of either vitamin E or a placebo each day. This treatment lasted for six months. Assessments of cognitive function of the patients were made at the beginning and at the end of the six-month trial period. Lloret and colleagues found that the patients receiving vitamin E could be separated into two smaller groups: vitamin E respondents and vitamin E non-respondents. The respondents were able to maintain their cognitive function throughout the trial. In contrast, a sharp decrease in cognition was observed in the patients that did not respond to vitamin E supplementation. The cognitive decline in these patients was more severe than the placebo group as well. The findings of this study indicated that vitamin E may be a beneficial treatment for patients with AD classified as vitamin E respondents but harmful to those classified as non-respondents (Lloret et al., 2009).

Dysken et al. observed contrasting results in their 2014 study on the effect of vitamin E and memantine on patients with mild to moderate AD. This study had 613 participants and was much larger than the study by Lloret et al. (2009). The patients were divided into four groups: a group receiving only vitamin E, a group receiving only memantine, a group receiving both vitamin E and memantine, and a placebo group receiving neither intervention. Dysken and colleagues assessed the participants using
measurements of ability to perform ADLs, global cognitive functioning, neuropsychiatric symptoms, caregiver burden, and functional dependence. At the conclusion of the study, the researchers found that the patients receiving vitamin E alone declined at a slower rate than patients in the three other groups as measured by the ability to perform ADLs. There were no significant differences observed for any of the other assessed outcomes, but there was a trend towards less decline of these measures when compared with the placebo group. Maintaining the ability to perform ADLs is beneficial for both economic cost and quality of life. Because vitamin E supplementation is very inexpensive, Dysken et al. (2014) noted that this intervention is likely to be economical.

**Omega-3 Fatty Acids**

Lipids are one of the main components of the central nervous system (CNS). In particular, omega-3 fatty acids play a large role in the normal function of the brain. High levels of omega-3 fatty acids are found in fish (Cederholm, Salem, & Palmblad, 2013). The most common omega-3 fatty acid in the brain is docosahexaenoic acid (DHA), which is a major component of neuronal membranes. Eicosapentaenoic acid (EPA) is another common omega-3 fatty acid that has a functional role in the central nervous system (Wu et al., 2015). Because of the important role of omega-3 fatty acids in the brain, it has been suggested that increasing the amount of omega-3 fatty acids in the diet may play a protective role in cognitive decline and may be beneficial for patients diagnosed with AD (Nelson & Tabet, 2015). There have been a number of clinical trials which were
performed to investigate the effect of omega-3 fatty acids on patients with AD (Chiu et al., 2008; Phillips, Childs, Calder, & Rogers, 2015; Quinn et al., 2010).

The 2008 study by Chiu et al. examined the effectiveness of an omega-3 polyunsaturated fatty acid (PUFA) supplementation as a means to slow the decline in patients with AD and MCI. Forty-six patients randomly placed in two groups, with one group receiving a dose of omega-3 PUFAs and the other group receiving an olive oil placebo were assessed periodically throughout the 24-week study. The researchers measured the patient’s global cognitive function using ADAS-cog and MMSE, clinical condition using the Clinician’s Interview-Based Impression of Change scale (CIBIC-plus), and depression using the Hamilton Depression Rating Scale (HDRS). Chiu and colleagues found that there was a beneficial effect on the CIBIC-plus score for the experimental group taking omega-3 PUFAs. There was no significant effect on either of the global cognition scales (ADAS-cog and MMSE); however, it was found that the participants with MCI showed a statistically significant improvement in ADAS-cog scores. From these results, the researchers concluded that omega-3 fatty acids potentially had a beneficial effect on clinical condition in AD and MCI patients. Furthermore, although no effect was found on cognition in AD patients, omega-3 fatty acids might have a beneficial cognitive effect in patients with MCI and very early AD (Chiu et al., 2008).

The study by Quinn et al. in 2010 investigated the effects of supplementation with DHA on patients with mild to moderate AD. In this study, 402 AD patients were assigned to two groups: one group of 238 receiving a supplement of DHA and one group
of 164 receiving a placebo. The purpose of the study was to observe the effect of DHA on the decline of cognitive function and functional ability. The treatment was administered to the participants for 18 months, with assessments occurring throughout the trial period. During these assessments, the researchers investigated the participant’s global cognition, ability to perform ADLs, neuropsychiatric symptoms, and quality of life. Brain volume was evaluated in a smaller group. The results of the study indicated that there was no detectable beneficial effect in patients taking the supplement of DHA compared with the control group for any outcomes. In the smaller group of patients receiving magnetic resonance imaging (MRI) to investigate the effect of DHA on brain volume, there was no slowing of brain atrophy with the supplementation of DHA (Quinn et al., 2010).
DISCUSSION

Cognitive Interventions for Alzheimer’s Disease

Based on the definitions from Borisovskaya et al. (2014), the interventions used by four of the seven reviewed studies tested a cognitive training (CT) intervention (Cahn-Weiner et al., 2003; Davis et al., 2001; Loewenstein et al., 2004; Niu et al., 2010). Two studies qualified as cognitive rehabilitation (CR) interventions (Clare et al., 2010; Kim, 2015), and one qualified as a cognitive stimulation (CS) intervention (Olazarán et al., 2004). All seven studies reported some benefits to the tested intervention, but most showed mixed and modest results.

Although the cognitive training studies of Davis et al. (2001), Cahn-Weiner et al. (2003), and Loewenstein et al. (2004) described benefits in recall with regard to face-name associations, it is unknown whether these benefits transfer to real-life situations or how long these effects last after the study. Also, there were no neuropsychiatric or ADL benefits found in any of these studies. On the other hand, the study by Loewenstein et al. (2004) showed evidence of benefits in practical functional skills such as paying bills and making change, which may benefit real-life scenarios. Unlike the other three cognitive training studies, Niu et al. (2010) showed possible benefits for neuropsychiatric symptoms, specifically with apathy and depression, unveiling a possible clinically relevant benefit to cognitive training. Furthermore, the results showed an improvement in MMSE for the group receiving cognitive training, which may indicate a possible benefit for global cognition (Niu et al., 2010).
The cognitive stimulation therapy by Olazarán et al. (2004) was the longest of the reviewed studies, lasting a full year. Over the year, AD patients were able to maintain ADAS-cog, a global cognition score, and improve in GDS score (J. Olazarán et al., 2004). The result that cognition was maintained despite the inevitable cognitive decline that comes with AD is evidence for a clinically relevant benefit for cognitive stimulation therapy.

The studies by Clare et al. (2010) and Kim (2015) both tested the effects of cognitive rehabilitation; however, the study by Kim tested cognitive rehabilitation in combination with cognitive training exercises. Both of these studies found an improvement in goal performance and satisfaction. In addition, Clare et al. (2010) found that the experimental group had a higher memory performance during the six-month follow-up after the completion of the trial. Because of the individualized, goal-orientated nature of cognitive rehabilitation, the benefits found in cognitive rehabilitation may transfer more easily to real-life settings.

Even though the benefits of cognitive intervention were mixed and often modest, it is clear that benefits do exist. Six of the reviewed trials had interventions lasting just 5-12 weeks (Cahn-Weiner et al., 2003; Clare et al., 2010; Davis et al., 2001; Kim, 2015; Loewenstein et al., 2004; Niu et al., 2010), whereas only one study had an intervention lasting an entire year (Olazarán et al., 2004). Therefore, it may be the case that stronger and more lasting benefits can be seen during longer-term studies. Additionally, none of the seven studies discussed the cost of cognitive interventions. Because cost is very
important when deciding which intervention to choose, more research on the cost
effectiveness of cognitive interventions for AD is necessary.

Finally, six of the seven reviewed studies indicated that the AD patients were
taking cholinesterase inhibitors (Cahn-Weiner et al., 2003; Clare et al., 2010; Davis et al.,
2001; Kim, 2015; Loewenstein et al., 2004; Niu et al., 2010; Olazarán et al., 2004), and
the remaining study did not disclose any information (Kim, 2015). It is unclear if the
results of these cognitive intervention studies would change if cholinesterase inhibitors
were not used; although ethically this question may not be answerable.

Due to the modest benefit seen in the cognitive interventions reviewed, more
research is necessary before cognitive interventions can be utilized daily for the treatment
of patients with AD.

Exercise Interventions for Alzheimer’s Disease

Out of the seven exercise intervention studies reviewed, six of them reported that
there was some kind of benefit in physical function for the group receiving the exercise
intervention (Holthoff et al., 2015; Miu et al., 2008; Rolland et al., 2007; Steinberg et al.,
2009; Venturelli et al., 2011; Vreugdenhil et al., 2012). This benefit in the physical
function of patients with AD may indicate an improvement in the ability to perform
activities of daily living. In fact, five of the seven studies used an assessment of the
patient’s ability to perform ADLs, and in these five studies an ADL benefit was found for
patients receiving the intervention (Holthoff et al., 2015; Rolland et al., 2007; Steinberg
et al., 2009; Venturelli et al., 2011; Vreugdenhil et al., 2012). Therefore, this review of
these seven studies suggests that an exercise program can significantly improve or at least slow the deterioration in physical ability and capacity to perform ADLs that is normally characteristic of patients with AD.

Next, five of the seven exercise intervention studies assessed the effect of exercise on the global cognition of the participants (Holthoff et al., 2015; Miu et al., 2008; Steinberg et al., 2009; Venturelli et al., 2011; Vreugdenhil et al., 2012). Out of these five studies, Venturelli et al. found a slowing of the cognitive decline, and Vreugdenhil et al. found increased cognition for the groups receiving the exercise intervention (Venturelli et al., 2011; Vreugdenhil et al., 2012). In the other three studies that assessed the cognition of the participants, the exercise programs had no effect on cognition (Holthoff et al., 2015; Miu et al., 2008; Steinberg et al., 2009). Because of these mixed results, no conclusion can be drawn about whether exercise interventions have a beneficial effect on global cognition for patients with AD.

Furthermore, studies have shown that exercise may have a protective effect against depression in patients with AD (Regan, Katona, Walker, & Livingston, 2005). Out of the seven studies reviewed, five assessed the participants for changes in depression (Holthoff et al., 2015; Miu et al., 2008; Rolland et al., 2007; Steinberg et al., 2009; Vreugdenhil et al., 2012). Only two of these five studies showed that an exercise intervention had a beneficial effect on depression (Holthoff et al., 2015; Vreugdenhil et al., 2012). Therefore, it is difficult to form an opinion about the impact of exercise on depression in AD patients.
The role that dementia medication like cholinesterase inhibitors and memantine play in the results of these seven studies is also unclear. Holthoff and colleagues reported that all of the participants used in their study were taking either cholinesterase inhibitors, memantine, or both (Holthoff et al., 2015). Three other studies stated that a portion of their participants were taking cholinesterase inhibitors (Miu et al., 2008; Rolland et al., 2007; Vreugdenhil et al., 2012). The other three studies did not mention whether the participants were taking dementia medication during the test (Cott et al., 2002; Steinberg et al., 2009; Venturelli et al., 2011). Because of this inconsistency, it may prove beneficial to evaluate the effect of an exercise intervention on AD patients with and without the use of dementia medication.

The lack of harmful side effects, the significant benefits on ADL and quality of life, and the cost effectiveness of home-based exercise programs are important factors which make exercise interventions a practical method for managing AD.

**Nutritional Interventions for Alzheimer’s Disease**

Although the research on the effects of the Mediterranean diet for patients with AD is lacking, the results from the study by Scarmeas et al. (2007) indicated a beneficial effect on mortality. It is clear that more research is necessary to verify this effect on patients with AD. Because maintaining a Mediterranean diet is safe, relatively easy, and potentially beneficial, it is a practical option for use in patients with AD.

Regardless of the negative results from the studies by Kwok et al. (2011) and Aisen et al. (2008), there is no doubt that supplementation with vitamins B12, B6, and
folic acid has a significant effect on the plasma level of homocysteine. As a result, more research needs to be done to investigate the possible benefits on patients with AD.

Based on the conflicting results of the two studies by Lloret et al. (2009) and Dysken et al. (2014), it is clear that more research on vitamin E supplements is necessary. If it is true that supplementation with vitamin E is a clinically beneficial intervention for patients with AD, then it seems worthwhile to pursue because of the inexpensive cost of vitamin E. On the other hand, additional scrutiny is necessary as a result of the finding that supplementation with vitamin E may potentially harm some AD patients.

Although the theory behind supplementation with omega-3 fatty acids in AD patients is logical, the clinical trials to date do not show compelling evidence for their use in slowing the decline in AD. However, because of the positive results found in some studies, further research is justified.
CONCLUSIONS

Although the three reviewed nonpharmacological interventions for AD—cognitive, exercise, and diet—found only modest benefits, some are promising, clinically relevant, and easy to put into practical use.

The cognitive intervention that had the most significant results was cognitive rehabilitation. This finding may be a result of the personalized approach taken by cognitive rehabilitation to focus on the needs and goals of each individual patient. It may be that focusing on each patient better prepares the individual to face his or her personal challenges. Although benefits of cognitive training and cognitive stimulation also were observed, the results were often modest and mixed.

Next, even though most exercise interventions did not have an effect on the cognitive decline characteristic of Alzheimer’s disease, most interventions were able to produce beneficial results in terms of physical function or ability to perform activities of daily living. Because much of the economic and social cost of Alzheimer’s disease comes from the patients’ inability to care for themselves, these positive findings regarding the physical functioning of AD patients are beneficial for the quality of life of the patients as well as their families. It is clear that exercise interventions are ready for implementation into widespread practice.

Finally, the results of the diet interventions were difficult to interpret given the mixed results of the reviewed clinical trials. However, there seem to be beneficial effects of maintaining the Mediterranean diet.
In conclusion, there are potentially significant clinical benefits from the three nonpharmacological interventions. With the increasing number of patients with Alzheimer’s disease and the relatively few successful treatments available to these patients, more research on nonpharmacological interventions is warranted.
FUTURE PLANS

Modest positive results were observed for all three nonpharmacological interventions reviewed; therefore, future studies are warranted on each of the three methods. More specifically, future randomized control trials are critical to verify the beneficial effects observed for cognitive rehabilitation. In addition, it was clear from the literature that exercise interventions for patients with AD had a positive effect on the ability of patients to perform ADLs, but it was unclear whether there was a specific effect on cognition. Consequently, further trials are essential to study the effect of exercise on cognition. Additionally, the Mediterranean diet was reported to have a beneficial effect on patients with AD; however, research on this topic was lacking and future trials are recommended.

In most of the studies reviewed in this thesis, the patients with AD were taking cholinesterase inhibitors throughout the duration of most experimental trials. This situation is not surprising because cholinesterase inhibitors are one of the few proven dementia medications. However, it would prove informative to observe the results of each nonpharmacological intervention without the use of cholinesterase inhibitors to complicate the findings.

Lastly, an intervention combining cognitive, exercise, and nutritional interventions is a warranted strategy. It would be interesting to observe the overall effect on global cognition as well as quality of life for patients with AD of a combinatorial
intervention including cognitive rehabilitation, moderate exercise, and a controlled Mediterranean diet.
REFERENCES


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Boston University School of Medicine, Boston, MA
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Inova Alexandria Hospital, Alexandria, VA
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• Stefano Agolini, M.D., General Surgeon, Observed multiple surgeries and rounded on surgical patients.
• Ashok Chauhan, M.D., Pulmonologist, Accompanied the physician on rounds.
• David Alway, M.D., Neurologist, Accompanied the physician on rounds.
• Arina Van Breda, M.D., Interventional Radiologist, Observed multiple imaging guided procedures including angioplasty and tumor ablation.

Georgetown University Hospital, Washington, DC
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• Dennis Murphy, M.D., Internist, Accompanied the physician during both diagnostic and well-office visits.

RESEARCH EXPERIENCE

National Institutes of Health -- National Institutes of Neurological Disorders and Stroke
Summer Intern, May 2013-August 2013
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• Researched the effects of alcohol on patients with essential tremor.
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• Created and presented medical posters to the NIH scientific community.

VOLUNTEER WORK

Arrupe International Immersion Program
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AWARDS

2013 • Exceptional Summer Student Award, NINDS, National Institutes of Health
2012 • Exceptional Summer Student Award, NINDS, National Institutes of Health

PUBLICATIONS