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A Systematic Review Comparison of Ketogenic Dietary Treatment Efficacy for Alzheimer's Disease

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University of Northern Colorado
Greeley, Colorado

A Systematic Review Comparison of
Ketogenic Dietary Treatment Efficacy for Alzheimer's Disease

A Thesis
Submitted in Partial
Fulfillment for Graduation with Honors Distinction and
The Degrees of Bachelor of Science

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December 2018

A Systematic Review Comparison of
Ketogenic Dietary Treatment Efficacy for Alzheimer's Disease

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Abstract

There is evidence suggesting that Alzheimer's disease (AD) pathology can be improved through the use of mechanistic/mammalian target of rapamycin (mTOR) inhibition therapy. Regulation of mTOR is responsible for mediating cell growth by regulating cell processes such as autophagy, transcription, and translation. Evidence suggests that a ketogenic dietary (KD) treatment may result in decreased mTOR signaling, thus making KD a potential treatment for AD. The objective of this systematic review was to explore the efficacy of current AD medications and compare the results to preliminary KD treatment for AD. The biochemical relevance of mTOR inhibition for AD and the relevance to KD will be discussed. For the purpose of this research 218 articles were identified in the original search, 14 studies met inclusion criteria for data compilation. A summary of the data and generalizability of the results are discussed. KD treatment and NMDA antagonists receptors were found to be more effective than acetylcholinesterase inhibitors.

Keywords: mTOR, ketogenic diet, donepezil, galantamine, memantine, rivastigmine, tacrine, and Alzheimer's disease.

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A Systematic Review Comparison of Ketogenic Dietary Treatment Efficacy for Alzheimer's Disease

Introduction

The purpose of this study is to explore the efficacy of the ketogenic diet (KD) treatment and current popular drug therapies for Alzheimer's Disease (AD) by reviewing current literature. KD therapy has presented evidence for many benefits including weight loss, anti-inflammatory properties, repair of insulin signaling, improved cardiac health, normalization of serum triglyceride levels, prevention and management of type 2 diabetes, improvement and prevention of neurological disorders, management of metabolic disorders, improved outlook for patients with cancer, treatment of obesity, management of chronic pain, anti-social and autistic behavioral improvement, and reduction of clinically severe acne (Masino & Ruskin, 2013; McClernon et al., 2007; Paoli et al., 2013; Veech et al., 2017; Vidali et al., 2015). The wide variety of benefits suggests that KD may be a useful intervention for a wide variety of diseases including Alzheimer's disease.

The KD treatment was first used as a novel treatment for epilepsy during the 1920's with promising results. Through restricting consumption of dietary glucose, the body enters a state termed nutritional ketosis. During nutritional ketosis, the body primarily utilizes dietary and stored fat as the main source of energy (rather than sugars). During nutritional ketosis the serum concentrations of ketone bodies (such as D- β -hydroxybutyrate) increase to partially replace glucose as a fuel source. KD treatment has expanded greatly beyond epilepsy treatment and shows promise for the treatment of many ailments (Masino & Ruskin, 2013; McClernon et al., 2007; Paoli et al., 2013; Veech et al., 2017; Vidali et al., 2015).

Despite promising therapeutic applications of KD, stigma surrounding the composition of the diet has led to discussion of the safety of KD treatment. Comparisons of nutritional ketosis to

diabetic ketoacidosis are commonly made by medical and nutritional professionals, but these comparisons are not supported by data (Freeman & Kossoff, 2010; Manninen, 2004). The stigma surrounding dietary fat consumption can be traced to the popularization of the dietary lipid hypothesis during the 1950's. The dietary lipid hypothesis states that high dietary fat consumption is detrimental for health. Ancel Keys was a researcher that advocated the dietary lipid hypothesis with the infamous "seven countries" study from 1970 (which has been discredited due to selective data presentation) (Pett, Kahn, Willett, & Kazi, 2017). The results of this study further fueled the stigma against dietary fat by identifying saturated fat as the main culprit of heart disease. Current evidence suggests no link between saturated fat consumption and heart disease (Chowdhury et al., 2014; Malhotra, Redberg, & Meier, 2017; Siri-Tarino, Sun, Hu, & Krauss, 2010). Concerns over adverse physiological impacts of KD treatment on liver, kidney, and neurological function have also been suggested, but are not supported by current data (Holland et al., 2016; Poplawski et al., 2011; Roy et al., 2015).

AD is a neurodegenerative disease that commonly affects the elderly. However, understanding the causes and origin of the disease pathology are not well understood. Current hypotheses include genetic causes, amyloid buildup, tau protein abnormalities, inflammation, and over-expression of mechanistic/mammalian target of rapamycin (mTOR) (Caccamo et al., 2013; Hardy, & Allsop, 1991; Heppner, Ransohoff, & Becher, 2015; Holmes, 2013; Mudher, & Lovestone, 2002; Wilson et al., 2011). There currently is no accepted cure or treatment to stop progression of the disease; however, KD treatment has produced positive results in human trials (Craft et al., 2016; Swerdlow, 2017). Results from mouse models are mixed (Beckett et al., 2013; Brownlow, Benner, D'Agostino, Gordon, & Morgan, 2013; Brownlow et al., 2013; Van der Auwera et al., 2005). Inhibition of the mammalian/mechanistic target of rapamycin (mTOR) has

also been suggested as a potential treatment (Cai, Chen, He, Xiao, & Yan, 2015; Wang et al., 2014). The mTOR kinase is responsible for controlling cellular growth and has a role in metabolism response (Hall, 2008). Limited evidence suggests that a KD treatment may improve the condition of patients with AD due to region-specific decline of brain glucose metabolism through mTOR inhibition (Lange et al., 2017; McDaniel, Rensing, Thio, Yamada, & Wong, 2011; Veech et al., 2017).

AD patient neurodegeneration is measured through cognitive impairment via tests. Two of the most popular tests are the Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog) (Kolibas, Korinkova, Novotny, Vajdickova, & Hunakova, 2000; Pangman, Sloan, & Guse, 2000). The MMSE is a questionnaire with a maximum of 30 points that measures functions such as language, memory, and spatial awareness. A higher score indicates less cognitive impairment. A score of 25 or above equates to normal cognition. The ADAS-Cog was originally developed by Rosen et al. and was modified to its currently used version by Mohs and colleagues (Mohs et al., 1997; Rosen et al., 1984). The ADAS-Cog measures cognition via a questionnaire with a minimum score of 100 points that assesses functions such as word recognition, orientation, and language. A higher score indicates more mistakes were made by the subject and therefore more cognitive impairment. A healthy individual is expected to have a score of 5 or less. The average score for patients diagnosed with AD is 31.

There are currently five common medications for the treatment of AD. These drug treatments act as acetylcholinesterase inhibitors or as *N*-methyl-D-aspartate (NMDA) receptor antagonists. The acetylcholinesterase inhibitors include donepezil, galantamine, rivastigmine, and tacrine. Acetylcholinesterase inhibitors benefit patients with AD by preventing

acetylcholinesterase from hydrolyzing acetylcholine (a neurotransmitter) which is necessary for nerve impulses and motor function. Patient decline is associated with a loss of neurons and lowering of acetylcholine levels. Memantine is an NMDA receptor antagonist that functions by reducing the hyperactivity of NMDA receptors. NMDA receptor hyperactivity promotes neuronal death through excitotoxicity which eventually leads to cognitive decline. However, the limited efficacy of these medications is concerning (Birks, & Grimley, 2015; Birks, & Harvey, 2003).

Literature Review

Introduction

The ketogenic diet (KD) was first reported in scientific literature during the 1920s for the treatment of epilepsy. Recently KD has been suggested to be a safe and effective alternative treatment option for several diseases (Paoli, Rubini, Volek, & Grimaldi, 2013). The diet has commonly been used for weight loss, anti-inflammatory properties, improvement of insulin signaling, improvement of cardiac health and serum triglyceride levels, diabetes prevention and treatment, improvement and prevention of neurological disorders, metabolic disorders, cancer, obesity, pain, behavioral improvement, and acne (Masino & Ruskin, 2013; McClernon et al., 2007; Paoli et al., 2013; Veech et al., 2017; Vidali et al., 2015). The diet consists of modifying food intake through low-carbohydrate consumption to induce nutritional ketosis (Rodrigues et al., 2017). During nutritional ketosis, the body begins using fat for energy production instead of glucose, leading to body-wide changes. The biochemical mechanisms responsible for these changes requires further study.

Biochemical Mechanism

During low carbohydrate consumption the body begins utilizing ketone bodies (β -hydroxybutyrate, and acetoacetate) for energy (Rodrigues et al., 2017). Ketone bodies are produced from fat supplied by dietary consumption or through stored adipose tissue. The state of ketosis emulates life extending properties of caloric restriction, potentially mediated through FOXO genes, and is well conserved among a variety of distant species (Veech et al., 2017). FOXO gene activation is associated with regulation of ROS (reactive oxidative species), however the mechanisms behind this function remains elusive (Dedkova & Blatter, 2014). This is likely an evolutionary response to prolong fertility during times of famine (Veech et al., 2017). This is supported by observations that ketone bodies may be the preferred fuel source by specific parts of the brain (Andrews, Russeth, Drewes, & Henry, 2009). This is understandable as dietary fat provides more stored energy than carbohydrates, and may be a more efficient fuel source (Andrews et al., 2009). β -Hydroxybutyrate production is a crucial component responsible for mediating some of the effects of ketosis; however, the mechanism of action for KD treatment expands beyond β -hydroxybutyrate (Achanta & Rae, 2017).

The mTOR kinase is a highly conserved gene among eukaryotes, originally found in yeast. Cell growth and metabolism are regulated by mTOR, which is a downstream target of the Ras and Akt pathways (Hall, 2008). This implicates mTOR overexpression as a potential cause of cancer, metabolic dysregulation, inflammatory diseases, and aging. The role of mTOR in cell growth and metabolism is well studied, however the body-wide role requires further research. KD is suggested to inhibit activation of mTOR, though the evidence is limited and mechanisms are poorly understood (McDaniel, Rensing, Thio, Yamada, & Wong, 2011; Veech et al., 2017).

Inflammation

Inflammation is a defensive response triggered by pro-inflammatory cytokines released by immune cells. When properly utilized by the body, an inflammatory response allows the immune system to better combat foreign invaders. Improper activation of this response leads to chronic inflammation, which has a severe role in many diseases including AD (Pan et al., 2011). Thus, treatments that target and reduce inflammation are a critical area of research for the prevention and treatment of disease. KD has shown promising results for reducing chronic inflammation, treating symptoms associated with inflammatory diseases, restoring immune cells, and improving wound healing.

Treatment with KD can reduce inflammation in subjects, through reduced expression of pro-inflammatory proteins. A ketogenic diet was reported to reduce expression of TNF- α , a pro-inflammatory cytokine, in C57Bl/6J mice (Selfridge et al., 2015). TNF- α is responsible for regulating immune cells. KD treatment in healthy male subjects can alter the TLR-4 signaling pathway to decrease expression of NF- κ B and thus reduce an inflammatory response (Paoli et al., 2015). KD resulted in decreased expression of IL-1b and TNF- α in a LPS (lipopolysaccharide) induced fever rat model (Dupuis, Curatolo, Benoist, & Auvin, 2015). In a three-week study of athletes, expression of IL-6, IFN- γ , and TNF- α were not significantly different between the KD and control group; however, the dietary ratios used may not have been appropriate for KD, and ketosis was never tested in the participants (Rhyu & Cho, 2014).

KD can have profound positive effects on the immune system and symptoms of patients with diseases related to inflammation. KD reversed overexpression of mTOR signaling, possibly through inhibition of the mTOR pathway, and stabilized levels of Treg and TH17 cells in children with intractable epilepsy (Ni et al., 2016). Through restoration of immune cell levels,

patient condition improved. KD treatment in Wistar rats resulted in faster healing, but there was no significant difference in leukocyte count between the ketogenic group and the control group (Peres, Nogueira, Guimaraes, Coasta, & Ribeiro, 2013). The dietary treatment was only applied for seven days, and ketosis was not tested in the rats. A ketogenic diet improved memory dysfunction and motor impairment caused by brain inflammation in EAE (experimental autoimmune encephalomyelitis) mice (Kim et al., 2012). Improvements were seen in the behavior of mice in a model of ASD (autism spectrum disorder) undergoing KD, possibly through the anti-inflammatory effects of KD (Ruskin, Murphy, Slade, & Masino, 2017). KD may be a useful treatment for inflammation-associated pain and several diseases with inflammatory aspects (Masino & Ruskin, 2013). Overall, treatment with a KD can improve conditions associated with inflammation and immune cell imbalance, and further study of the mechanisms of action is necessary.

Therapeutic Uses of KD

Alzheimer's disease is a degenerative disease that affects the brain resulting in symptoms such as memory loss, dementia, and confusion among other symptoms. The origin of the disease is debated with current hypotheses including genetic predisposition, tau protein tangles, a buildup of amyloid protein, neurological inflammation, and mTOR over-expression (Caccamo et al., 2013; Hardy, & Allsop, 1991; Heppner, Ransohoff, & Becher, 2015; Holmes, 2013; Mudher, & Lovestone, 2002; Wilson et al., 2011). The literature does not currently report a treatment for the disease, but certain methods for potential treatment have been identified. Common drugs to treat AD include donepezil, galantamine, memantine, rivastigmine, and tacrine. These medications act as acetylcholinesterase inhibitors (with the exception of memantine which is an

NMDA antagonist). The efficacy of these medications has been questioned, suggesting the need for alternative treatments (Birks, & Grimley, 2015; Birks, & Harvey, 2003).

A large variety of approaches for AD treatment has been explored in the literature. However, many approaches attempt to eliminate existing plaques rather than prevent the formation of plaques (Folch et al., 2016). The use of multi-target-directed ligands to prevent plaque formation as a treatment has been explored (Bejda, Guzior, Ignasik, & Malawska, 2011). Inhibition of mTOR has also been researched (Cai, Chen, He, Xiao, & Yan, 2015; Wang et al., 2014). The mTOR kinase is a regulator of cellular growth and nutritional metabolism (Hall, 2008). Some research presents evidence that KD treatment may inhibit mTOR activation and improve the condition of patients through correction of glucose metabolism (Lange et al., 2017; McDaniel, Rensing, Thio, Yamada, & Wong, 2011; Veech et al., 2017). The biochemical mechanisms behind the effects of KD on mTOR are poorly understood and require more study.

Cancer is a disease with great variability in pathology. Many cancers can be treated (to some extent) through mTOR inhibition therapy including renal cell carcinomas, breast cancers, neuroendocrine tumors, and hematological malignancies (Mita, Mita, & Rowinsky, 2016). This suggests that despite the difficulties in treatment (due to rapid adaptation by tumors), overexpression of mTOR may be a common sign of unregulated cell proliferation. Treatment with KD can inhibit tumor growth and increase survival time in humans and animal models, but the mechanism is poorly studied (Khodadadi et al., 2017; Klement, Champ, Otto, & Kammerer, 2016). A suggested mechanism of action for these improvements is through insulin inhibition (Paoli et al., 2013). A relationship between cancer and inflammation is well established and plays a major role in disease pathology and patient outcome (Munn, 2017). KD may also be useful as a co-adjuvant therapy for cancer treatment by improving patient symptoms and

potentially sensitizing cancer cells to chemotherapy and radiation (Allen et al., 2014; Branco et al., 2016). KD can also help with the pain experienced by traditional cancer therapy patients, potentially through reduction of inflammation (Masino & Ruskin, 2013). The similarities between cancer and AD include metabolic dysregulation, improvement with mTOR inhibition therapy, and improvement with reduction of inflammation.

Diabetes is a growing epidemic in many countries around the world. Some researchers believe that AD is a form of diabetes (Accardi et al., 2012; Kandimalla, Thirumala, & Reddy, 2017). High consumption of sugar in beverages has been linked to T2D (type 2 diabetes) in the United States and Europe, suggesting that dietary sugar may increase risk of metabolic disorders (Wang, Yu, Fang, & Hu, 2015). Research for treatments targeting the cause of diabetes is a growing priority. KD treatment is effective in weight loss, improvement of glycemic control, and has good tolerance for patients with T2D when compared to a caloric restriction diet (Goday et al., 2016). The metabolism altering effects of the diet, and impact on insulin signaling, may be responsible for improvement of T2D patients (Branco et al., 2016; Paoli et al., 2013; Vidali et al., 2015). KD has also been used to successfully improve the condition of patients with type one diabetes mellitus (Aguirre-Castaneda, Mack, & Lteif, 2012; Dressler et al., 2010; Millichap, 2010). This suggests potential for KD as a prevention and treatment for multiple types of diabetes. Kidney failure is often seen in late-stage diabetic patients and is difficult to treat. Late-stage CKD (chronic kidney disease) patients showed improvements in thyroid function, blood pressure, and delayed CKD progression with KD (Jiang, Zhang, Yang, Li, & Qin, 2016). This suggests that cellular repair mechanisms, enabled by KD treatment, may reverse some damage associated with diabetes. Thus, KD has potential for the prevention, management, and treatment for various types of diabetes.

Links between obesity and AD and obesity and diabetes have been established (Bostock-Cox, 2017; Verdile et al., 2015). Obesity is a growing pandemic in desperate need of treatments that target the causes of obesity, not just the symptoms. As the number of obese individuals continues to grow, the rate of diseases associated with obesity will also grow. KD can enhance metabolic and cardiovascular health by improving blood triglyceride and cholesterol levels (Paoli et al., 2013; Paoli et al., 2015). KD treatment (started pre- or post-stroke) improves patient condition after suffering a stroke (Gibson, Murphy, & Murphy, 2012). In addition to weight loss, KD treatment can also suppress appetite, which may help patients control their diet (Gibson et al., 2015). Thus, KD treatment can be a low-risk substitute for bariatric surgery. Interestingly a KD diet was a better treatment of obesity than a low-fat diet (Paoli, 2014; Yancy, et al., 2004). A grain-rich, low-fat diet is often recommended as a healthful diet by medical experts. This suggests an inherent misunderstanding of the role of fats and carbohydrates in nutrition, however, this is beyond the scope of this review.

KD dietary treatment was originally used to treat epilepsy and has been used successfully to treat intractable childhood epilepsy (Vidali et al., 2015). KD treatment improved patients with intractable childhood epilepsy through restoration of Treg and TH17 cells (Ni et al., 2016). Anti-inflammatory benefits of KD treatment may also play a role in patient improvement (Ruskin et al., 2017). Insulin inhibition and associated metabolic improvement from KD may be responsible for these effects as well (Branco et al., 2016). The changes to metabolism brought on through KD treatment may also play a role in treating epilepsy (Masino, & Rho, 2018). Changes to the gut biome caused by KD may also be responsible for improvements (Zhang et al., 2018). Interestingly, some research suggests that mTOR inhibition can improve the condition of patients with epilepsy (Sadowski, Kotulska-J óźwiak, & J óźwiak, 2015). KD as a treatment for epilepsy

is well established, safe, and can even have comparable efficacy to antiepileptic drugs (Paoli et al., 2013).

A link between epilepsy and autism has been established, suggesting that both diseases may operate through related mechanisms (Levisohn, 2007). Autism afflicts patients from early childhood and creates difficulties in communication, impaired development of social skills, and other neurological defects. Improvements were seen in the behavior of mice in a MIA (maternal immune activation) model of ASD (autism spectrum disorder) undergoing KD treatment (Ruskin et al., 2017). BTBR mice showed similar improvements in autistic behavior, independent from anti-seizure effects, with KD (Ruskin et al., 2013). This suggests that mechanisms of KD have beneficial effects on patients with autism. KD treatment has been suggested to improve autistic behavior through neuronal improvement mediated by increased neuroprotective agents (Paoli et al., 2013). KD treatment as a therapy option for Alzheimer's, Parkinson's, MS (multiple sclerosis), sleep disorders, neurotrauma, ALS (amyotrophic lateral sclerosis), and GLUT 1 deficiency is promising; however, more research into the underlying mechanism of ketosis is necessary (Branco et al., 2016; Castro et al, 2015; Kim et al., 2012; Paoli et al., 2013; Vidali et al., 2015).

Many of the medical conditions covered in this review are complicated diseases that require complex cures, and AD is no exception. However, the ketogenic dietary treatment represents a simple and safe supporting intervention for the management of several inflammatory-based diseases, metabolic disorders, neurological disorders, and unregulated cellular proliferation. These symptoms are characteristic of AD and other common diseases. KD raises levels of ketone bodies (namely β -hydroxybutyrate), which demonstrate anti-inflammatory (through reduction of pro-inflammatory cytokines) and life-prolonging (through activation of

FOXO genes) properties as well. This suggests a KD treatment is generally safe and has multiple physiological benefits beyond disease treatment. For the best use of KD as a treatment, further review of the literature to establish biochemical mechanisms and pathways is crucial. This will allow viable insight into potential uses for KD, as well as identifying the limitations of this intervention.

Methods

Search Strategy and Study Selection

Electronic searches of PubMed, and UNC Summon were performed. There were 218 articles identified using search terms as ketogenic diet, drug efficacy, and Alzheimer's disease. Review articles and articles in languages other than English were excluded from the systematic review data analysis due to the possibility of translational errors and potential bias. The abstract of individual studies was carefully assessed for relevance to the research question to determine inclusion in the study. Relevant studies had quality assessed based on the merits of methodology which include the quality of patient compliance, data collection, participant recruitment, consistent dosage, and conflicts of interest. Studies of poor quality were excluded. Only studies measuring cognition with MMSE or ADAS-Cog assessments were included for consistent efficacy comparison. Drug efficacy trials with $N < 18$ were also excluded to reduce the possibility of skewed distribution in data due to small sample size (this search criterion was not applied to KD studies due to the limited number of studies available). Drug efficacy trials using multiple drugs or mixed interventions were excluded in order to obtain accurate measurement of individual treatment efficacy. Drug efficacy trials lasting less than six months were excluded to more accurately determine long-term (greater than six months) treatment efficacy (this search criterion was also not applied to KD studies due to the limited number of studies). KD studies not confirming nutritional ketosis via physiological measurement (e.g., urine measurement of ketone levels) were excluded. KD studies in which diet compliance was self-reported were excluded. Studies that passed the search criteria were compiled for inclusion in the literature review or reviewed for data analysis.

Data Collection and Analysis

After preliminary screening of articles was concluded, fourteen articles were kept for data analysis. A total of eight donepezil studies were analyzed (Aguglia, Onor, Saina, & Maso, 2004; Borkowska, Ziolkowska-Kochan, & Rybakowski, 2005; Pakdaman et al., 2015; Persson et al., 2009; Raquena, Santoro et al., 2010; Maestu, Campo, Fernandez, & Ortiz, 2006; Wallin et al., 2007; Zhang et al., 2015). A total of three galantamine studies were analyzed (Aguglia, Onor, Saina, & Maso, 2004; Santoro et al., 2010; Wallin, Wattmo, Minthon, & Klinisk, 2011). A total of two memantine studies were analyzed (Shiryaev et al., 2017; Zhang et al., 2015). A total of six rivastigmine studies were analyzed (Aguglia, Onor, Saina, & Maso, 2004; Borkowska, Ziolkowska-Kochan, & Rybakowski, 2005; Grossberg et al., 2004; Miettinen et al., 2015; Minthon et al., 2009; Santoro et al., 2010). A total of one tacrine study was analyzed (Wallin et al., 2004). A total of one KD study was analyzed (Taylor, Sullivan, Mahnken, Burns, & Swerdlow, 2018). Average MMSE and/or ADAS-Cog scores were extracted from studies and compiled. Only scores from compliant participants were used. Combined scores from compliant and dropout participants were not used. After consultation with the UNCO Research Consulting Lab, it was determined that statistical analysis was not a reasonable presentation of the compiled data. Due to the variability of compiled data (differing measurement times, differing trial length, and differing baseline scores) data was analyzed graphically rather than through advanced statistical methods. Therefore, the data were compared graphically and presented as such. Scores were plotted against time. The changes in score were plotted against time. The average change in score per month was calculated for each study's trial. These scores were compiled and compared across studies and treatments.

Results and Discussion

The KD trial had one series which had nine participants (Taylor et al., 2018). The first three months of the KD trial were during the KD intervention and the fourth month was during a washout where participants returned to a standard diet. During the KD treatment the recorded patient MMSE scores were found to increase. During the one month washout period the recorded patient MMSE scores were shown to decrease. The one month washout period after KD treatment appeared to worsen patient cognition. This suggests that the improvement brought on through the KD treatment was reversed once treatment discontinued. The KD MMSE data are presented in Figure 1. The KD ADAS-Cog data show similar trends of improving score during KD treatment and declining cognition during the washout period. The KD treatment appeared to improve patient cognition according to both MMSE and ADAS-Cog scores shown in Figures 1 and 2, respectively. The KD treatment shows the effect of improving patient cognition.

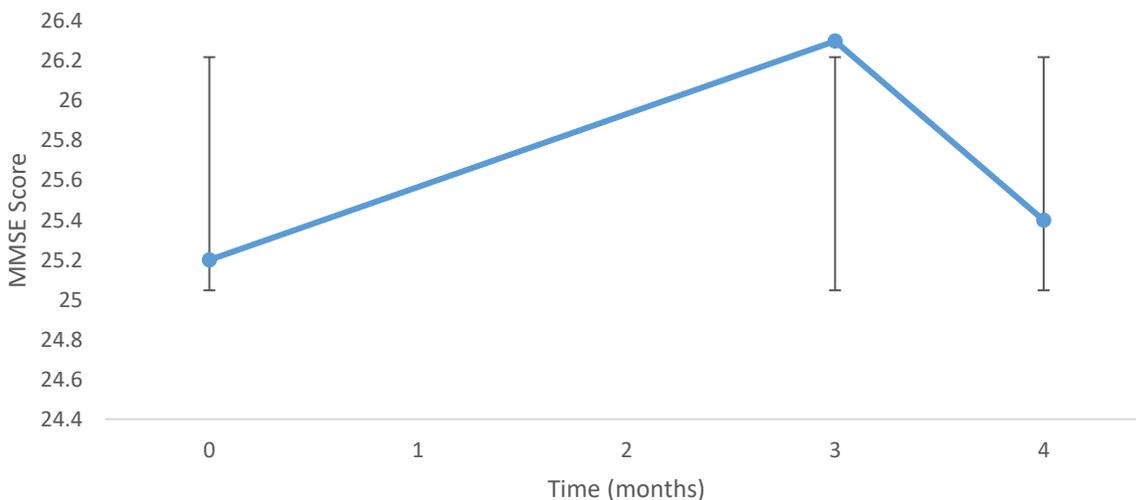


Figure 1: MMSE score changes measured during the KD treatment. The treatment was applied to participants through month 3. Month 3 through 4 was a washout period during which participants returned to a standard diet.

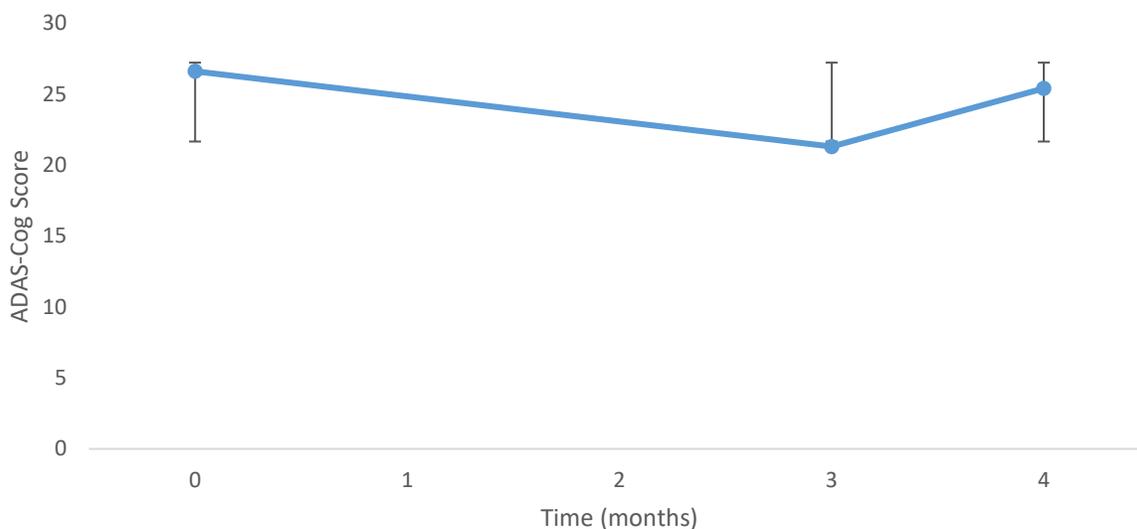


Figure 2: ADAS-Cog score changes measured during the KD treatment. The treatment was applied to participants through month 3. Month 3 through 4 was a washout period during which participants returned to a standard diet.

The donepezil trials had eight series. Series 1 had 47 participants (Borkowska, Ziolkowska-Kochan, & Rybakowski, 2005). Series 2 had 70 participants (Aguglia, Onor, Saina, & Maso, 2004). Series 3 had 158 participants (Persson et al., 2009). Series 4 had 491 participants (Santoro et al., 2010). Series 5 had 20 participants (Raquena, Maestu, Campo, Fernandez, & Ortiz, 2006). Series 6 had 87 participants (Zhang et al., 2015). Series 7 had 421 participants (Pakdaman et al., 2015). Series 8 had 435 participants (Wallin et al., 2007). Most of the donepezil series showed a decrease in MMSE scores including series 1, series 3, series 4, series 5, and series 8. Series 2 showed minimal change in MMSE scores. Series 6, and series 7 showed increases in scores. The ADAS-Cog scores reinforce these observations. Series 8 showed an initial MMSE increase at two months followed by a large decrease. The ADAS-Cog scores for this series did not demonstrate this initial increase in cognition, only a decline. The large study sizes for series 6, and series 7 (n=87, and n=421, respectively) support the validity of the outcome of these two series. It is relevant to note that the largest sample sizes for donepezil belonged to series 4, and series 8 (n=491, and n=435 respectively) which both showed worsening

of patient condition. The longest series were series 4 and series 7, both lasting 36 months. The largest MMSE decrease came from series 1 and the largest increase came from series 6. The donepezil MMSE data and ADAS-Cog data are presented in Figures 3 and 4, respectively. Series 1 did not contain ADAS-Cog scores and was not included in Figure 4.

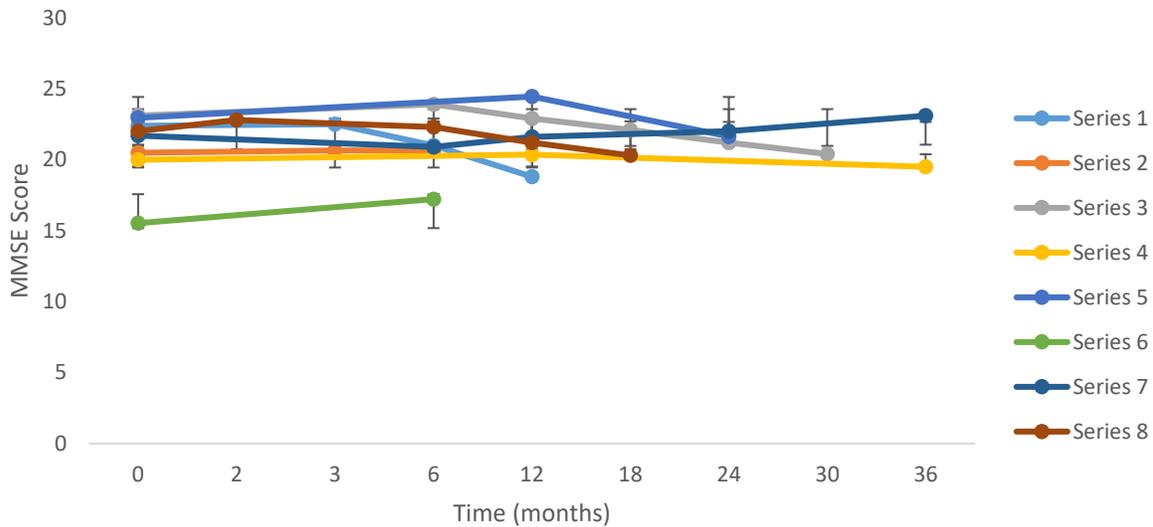


Figure 3: MMSE score changes measured during the donepezil treatment.

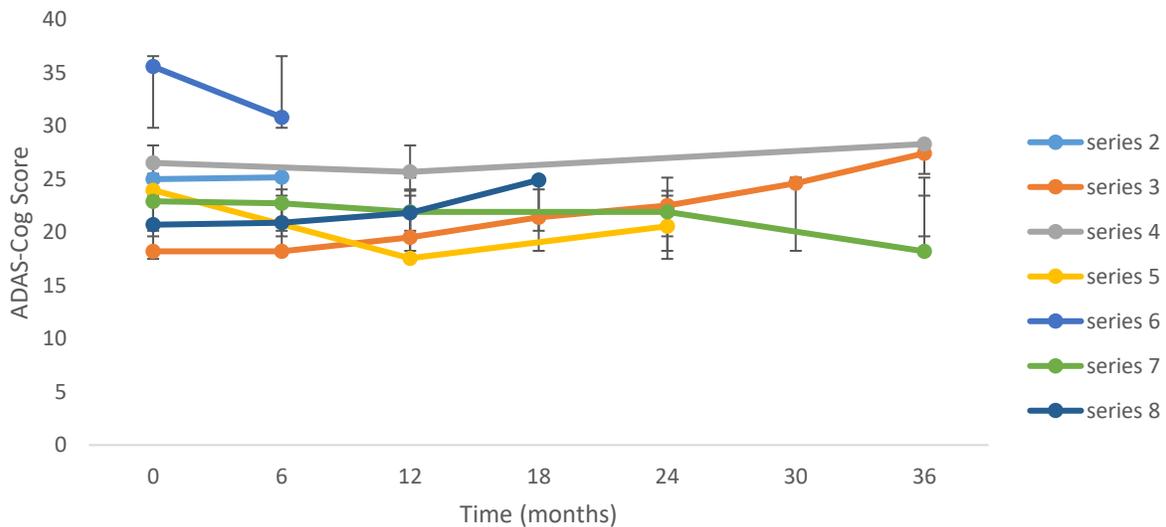


Figure 4: ADAS-Cog score changes measured during the donepezil treatment.

The galantamine trials had three series. Series 1 had 51 participants (Aguglia, Onor, Saina, & Maso, 2004). Series 2 had 94 participants (Santoro et al., 2010). Series 3 had 280

participants (Wallin, Wattmo, Minthon, & Klinisk, 2011). The galantamine treatments showed either no change or a decrease in cognition according to MMSE and ADAS-Cog scores. The galantamine MMSE and ADAS-Cog data are presented in Figures 5 and 6, respectively.

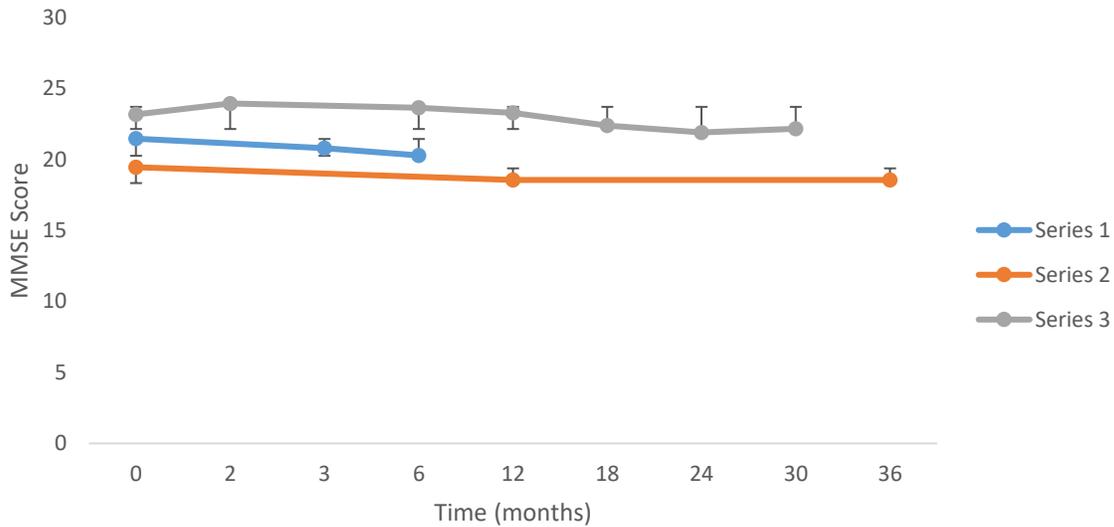


Figure 5: MMSE score changes measured during the galantamine treatment.

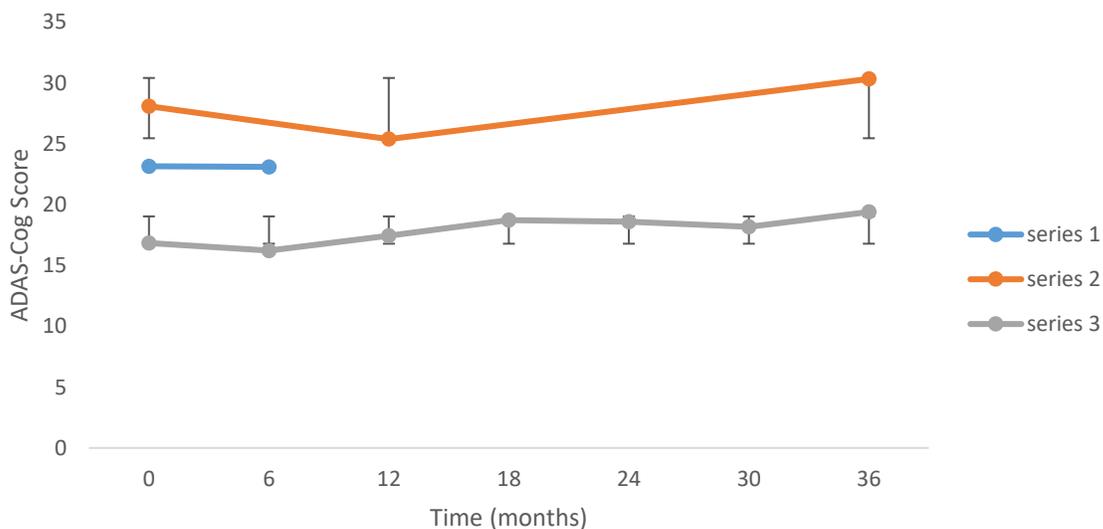


Figure 6: ADAS-Cog score changes measured during the galantamine treatment.

The memantine trials had two series. Series 1 had 25 participants (Shiryaev et al., 2017). Series 2 had 80 participants (Zhang et al., 2015). The memantine treatments showed an increase in cognitive condition according to MMSE and ADAS-Cog scores for both series. The

memantine MMSE and ADAS-Cog data are presented in Figures 7 and 8, respectively. Series 1 did not contain ADAS-Cog scores and was not included in Figure 8. The observed increases in cognition from memantine treatment suggest that NMDA receptor antagonist treatment for AD has strong efficacy.

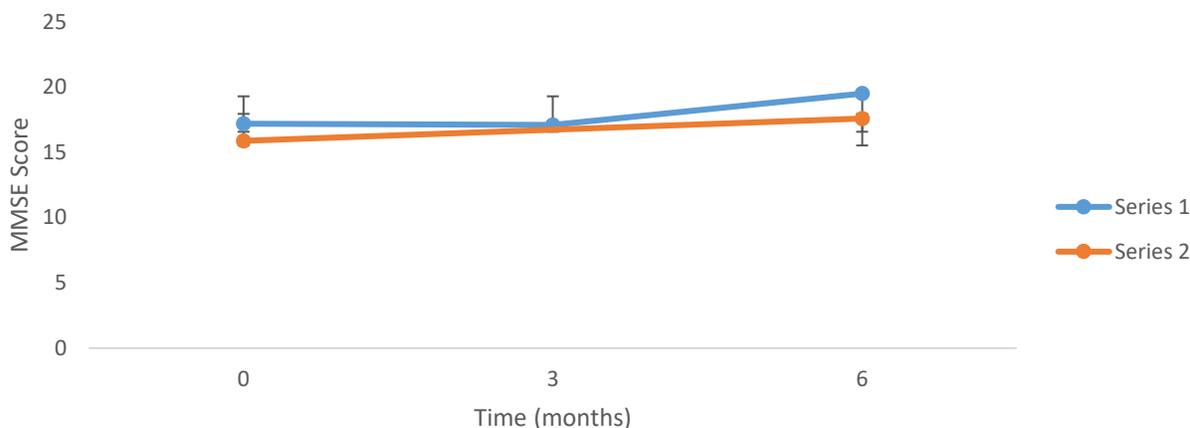


Figure 7: MMSE score changes measured during the memantine treatment.

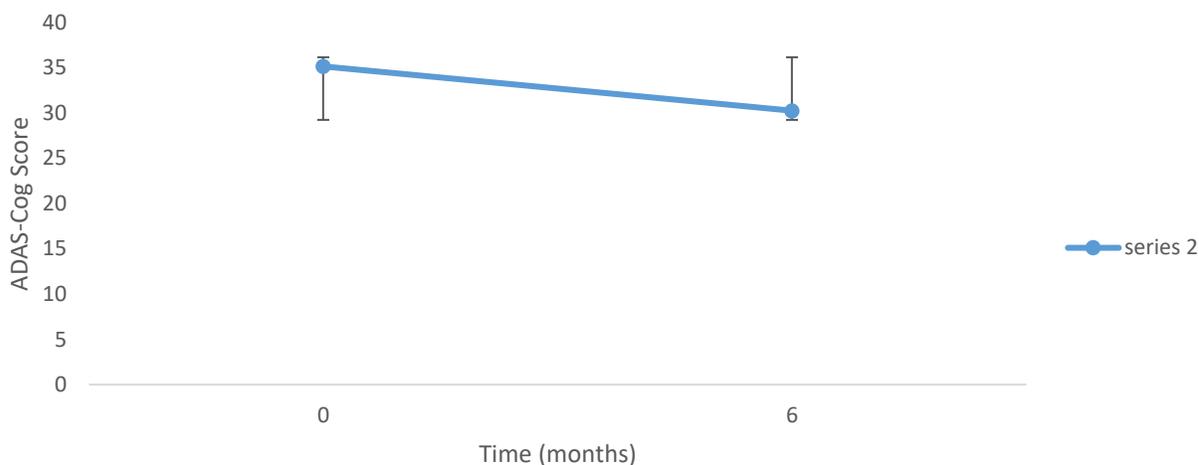


Figure 8: ADAS-Cog score changes measured during the memantine treatment.

The rivastigmine trials had six series. Series 1 had 29 participants (Borkowska, Ziolkowska-Kochan, & Rybakowski, 2005). Series 2 had 121 participants (Aguglia, Onor, Saina, & Maso, 2004). Series 3 had 234 participants (Santoro et al., 2010). Series 4 had 18 participants (Miettinen et al., 2015). Series 5 had 2010 participants (Grossberg et al., 2004).

Series 6 had 217 participants (Minthon et al., 2009). The rivastigmine treatments appeared to have limited efficacy. Minimal changes are observed in MMSE scores except for series 5 which decreased. More variety is shown in ADAS-Cog scores. Series 1, series 3, and series 4 showed initial cognitive improvement at 6 months and then cognitive decline. Series 2 showed a decline in ADAS-Cog scores at 6 months but has no data points past this time. Series 6 shows a gradual decrease in ADAS-Cog scores. The rivastigmine MMSE and ADAS-Cog data are presented in Figures 9 and 10, respectively. Series 5 did not contain ADAS-Cog scores and was not included in Figure 10.

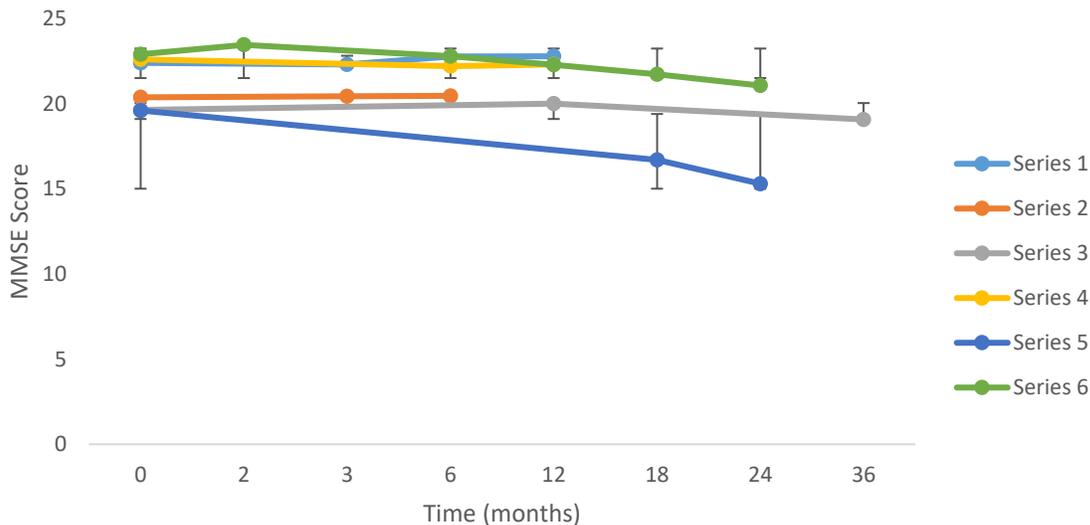


Figure 9: MMSE score changes measured during the rivastigmine treatment.

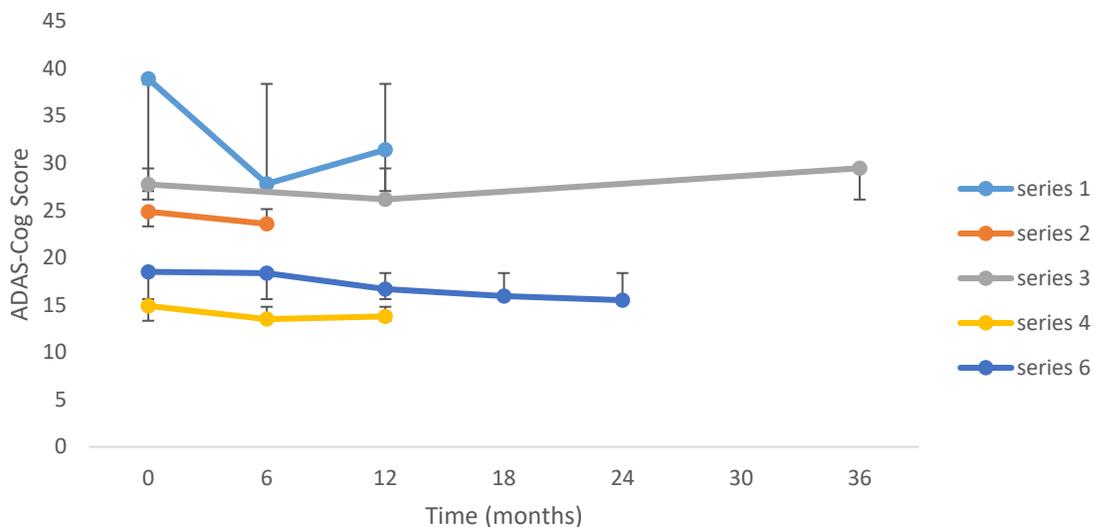


Figure 10: ADAS-Cog score changes measured during the rivastigmine treatment.

The tacrine trial had one series which had 50 participants. The tacrine study showed initial cognitive decline followed by an increase in MMSE scores at 36 and 48 months. This was followed by a decline at 60 months. The ADAS-Cog scores showed a similar trend with improvement being seen at 36 months. No ADAS-Cog scores were collected past 36 months in this study. The tacrine MMSE and ADAS-Cog data are presented in Figures 11 and 12, respectively.

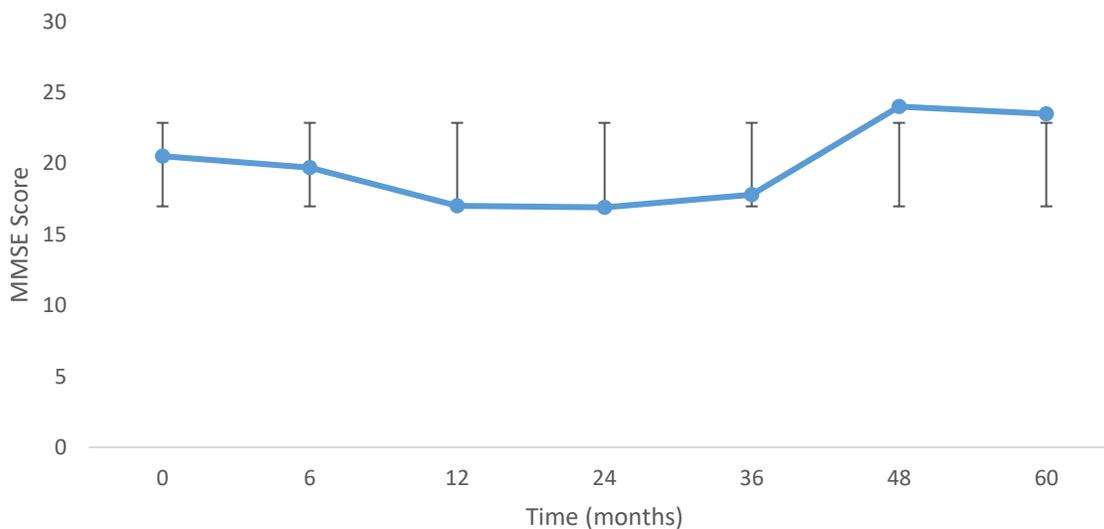


Figure 11: MMSE score changes measured during the tacrine treatment.

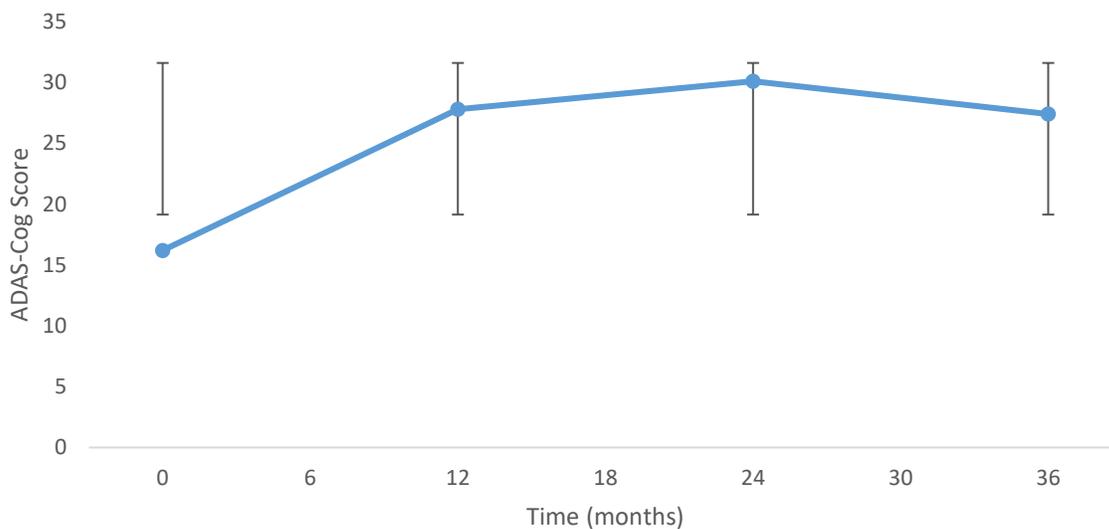


Figure 12: ADAS-Cog score changes measured during the tacrine treatment.

The MMSE score changes from baseline for donepezil treatment showed various results. Series 2, 6, and 7 showed an improvement. Series 5 showed an initial improvement followed by a steep decline after 12 months. Series 1, 3, 4, 5, and 8 showed an overall decline in cognition. The ADAS-Cog scores showed similar variability. The greatest ADAS-Cog decline came from series 3 and the greatest improvement came from series 5 at 12 months, but the magnitude of this change decreased at the next measurement occurring at 24 months. Series 7 had the greatest long-term decrease in ADAS-Cog scores with measurements taken at 6, 12, 24, and 36 months. Collectively these data show mixed results from donepezil. Figure 13 shows the change from baseline MMSE score against time in months and Figure 14 shows the change from baseline ADAS-Cog score against time in months, respectively, for the donepezil treatment trials.

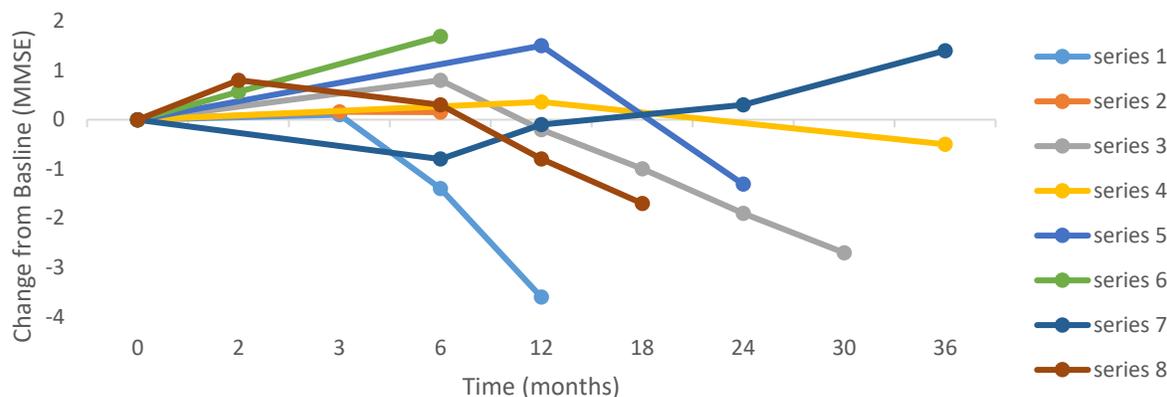


Figure 13: The change from baseline MMSE score was plotted against time in months for the donepezil treatments.

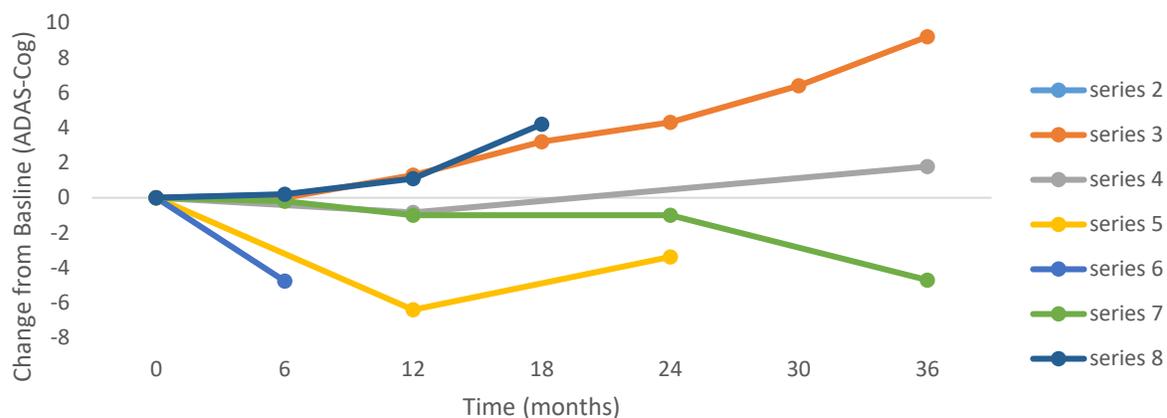


Figure 14: The change from baseline ADAS-Cog score was plotted against time in months for the donepezil treatments.

The change in MMSE scores during galantamine treatment for series 1, and series 3 appeared to decrease. The change from baseline of series 2 appeared steady. The change from baseline of ADAS-Cog scores suggests cognitive decline in series 2 and series 3. Series 1 did not collect enough ADAS-Cog measurements to make an accurate judgment of the change. The largest series was series 3 with n=280. The longest study was series 2 at 36 months followed by series 3 at 30 months. Overall these results appear to suggest minimal harm and minimal improvement of cognition over the course of years. Galantamine may show some prevention of cognitive decline during long term treatment, however more evidence would be required to assert

this claim. The decline in ADAS-Cog scores suggest this maintenance may be a limitation of the MMSE test rather than true cognitive protection. It is important to note that this data was only compiled from 3 studies. The data for the change from baseline scores for MMSE and ADAS-Cog during galantamine treatment are presented in Figures 15 and 16, respectively.

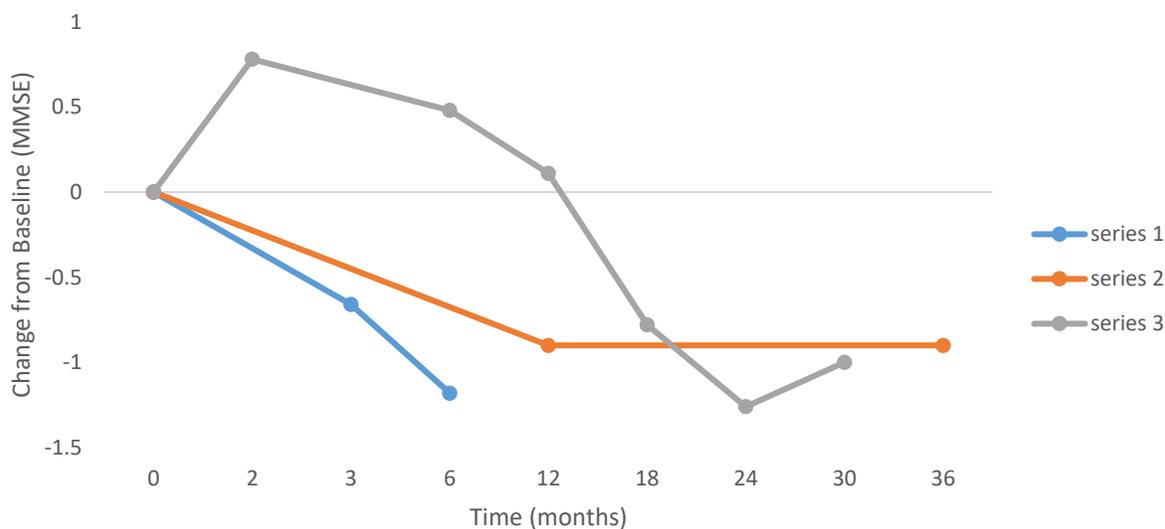


Figure 15: The change from baseline MMSE score was plotted against time in months for the galantamine treatments.

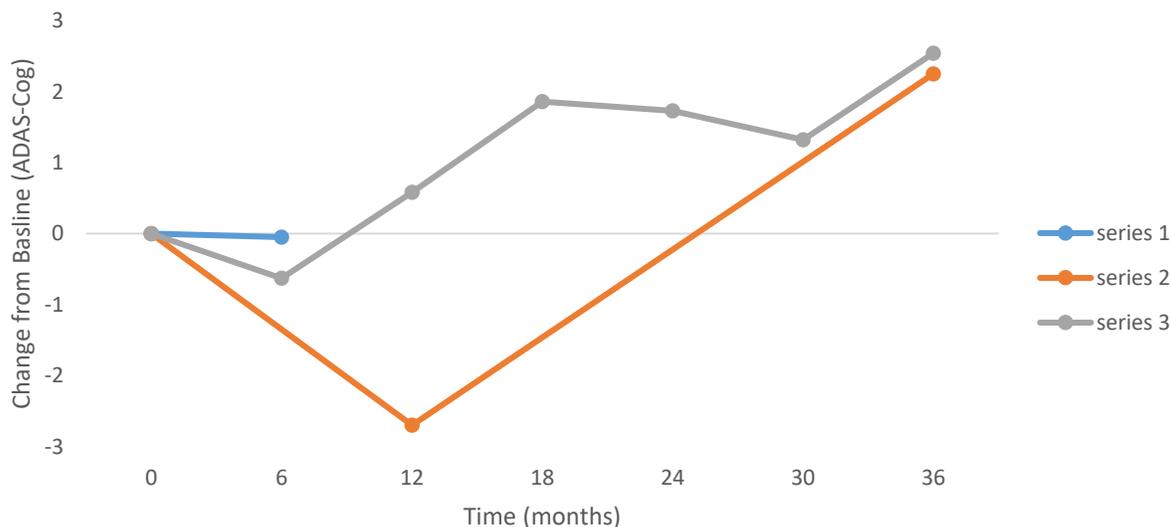


Figure 16: The change from baseline ADAS-Cog score was plotted against time in months for the galantamine treatments.

A large increase for both series of memantine was observed with series 1 having the greatest improvement. Series 2 had a single data point which shows a decrease in ADAS-Cog

scores. Series 2 had the largest sample size with n=80 and series 1 had the smallest with n=25. Both studies only lasted 6 months. The limited number of studies, the short duration of studies, and the small sample size suggest that the data collected should be approached cautiously. More evidence is required to support the benefits of memantine treatment, however these preliminary results show great promise. Figures 17 and 18 show the change from baseline MMSE score against time and the change from baseline ADAS-Cog score against time, respectively, for the memantine treatment trials.

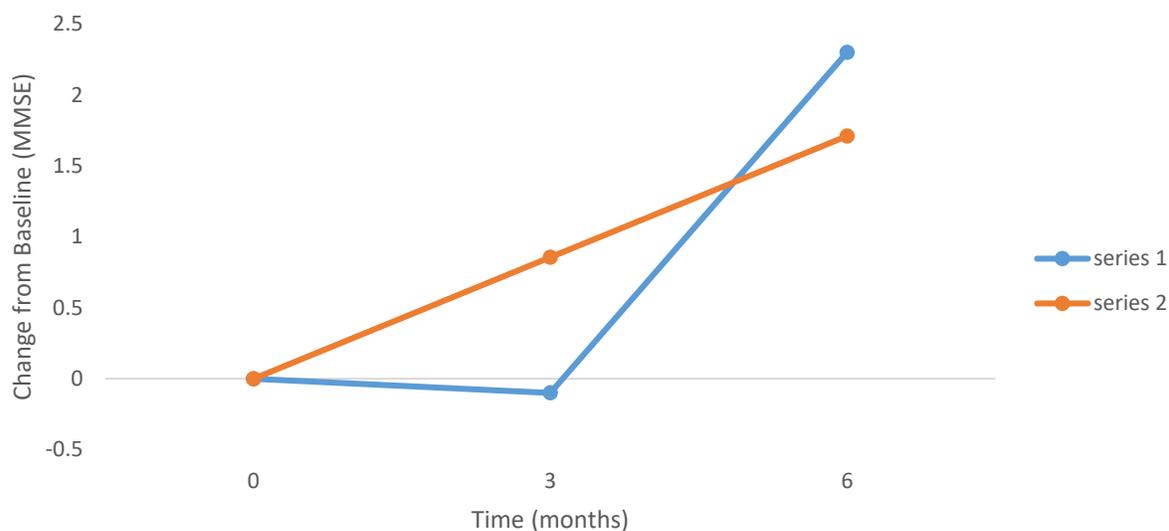


Figure 17: The change from baseline MMSE score was plotted against time in months for the memantine treatments.

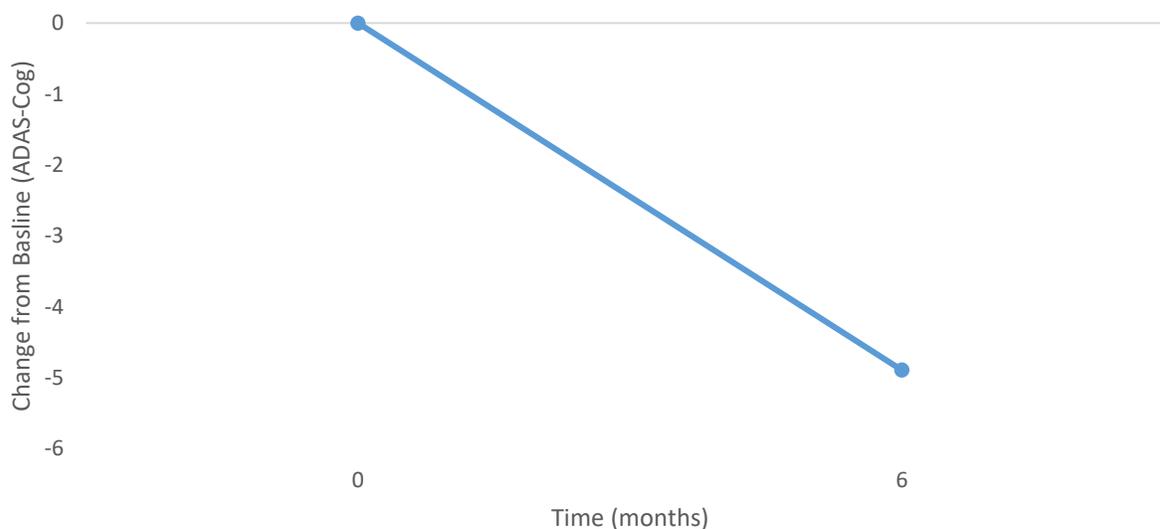


Figure 18: The change from baseline ADAS-Cog score was plotted against time in months for the memantine treatments.

Decreases from MMSE baseline score for were observed for rivastigmine treatment in series 3, series 5, and series 6. Series 1, series 2, and series 4 showed increases in MMSE scores. Series 5 showed the greatest decrease in MMSE scores and series 1 showed the greatest increase in MMSE scores. ADAS-Cog score increases were observed for series 1, series 3, and series 4. Series 2 did not have enough data points to suggest a trend. Series 6 showed a cognitive increase. The longest study was series 3 at 36 months followed by series 5, and series 6 at 30 months. The largest series was series 5 with n=2010 followed by series 3 with n= 234 and series 6 with n=217. Interestingly the 3 largest and longest series (3, 5, and 6) all showed cognitive declines through decreased MMSE scores. Series 3, and series 6 both showed cognitive declines through increased ADAS-Cog scores. Series 5 did not measure ADAS-Cog scores. The large sample sizes in these studies support the accuracy of the data. This data suggests there may be a short term improvement offered by rivastigmine (6 months). However, the long term efficacy of this treatment does not show promise. The change from baseline MMSE score against time and the change from baseline ADAS-Cog score against time are presented in Figures 19 and 20, respectively for the rivastigmine treatment trials.

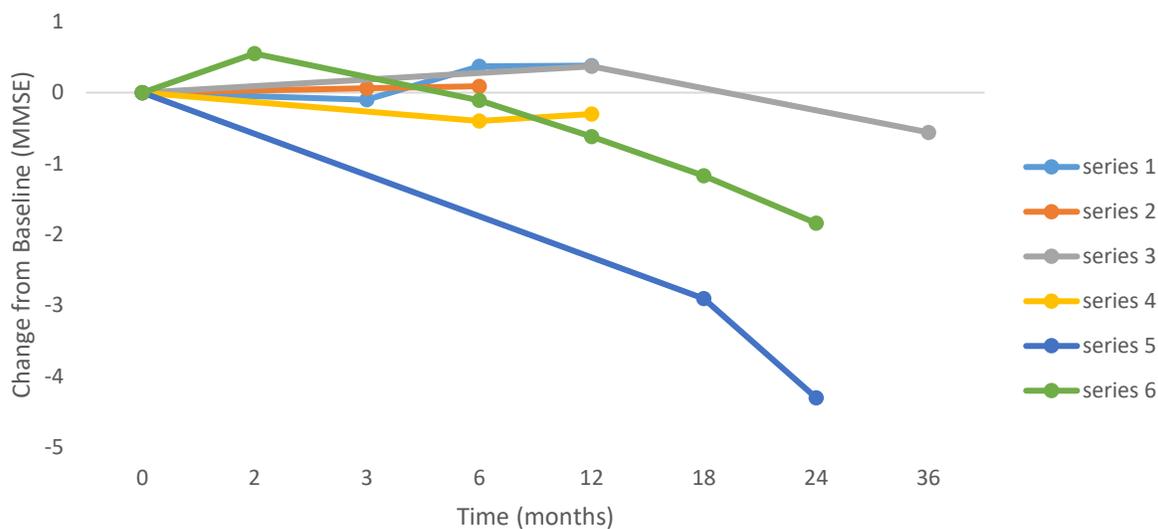


Figure 19: The change from baseline MMSE score was plotted against time in months for the rivastigmine treatments.

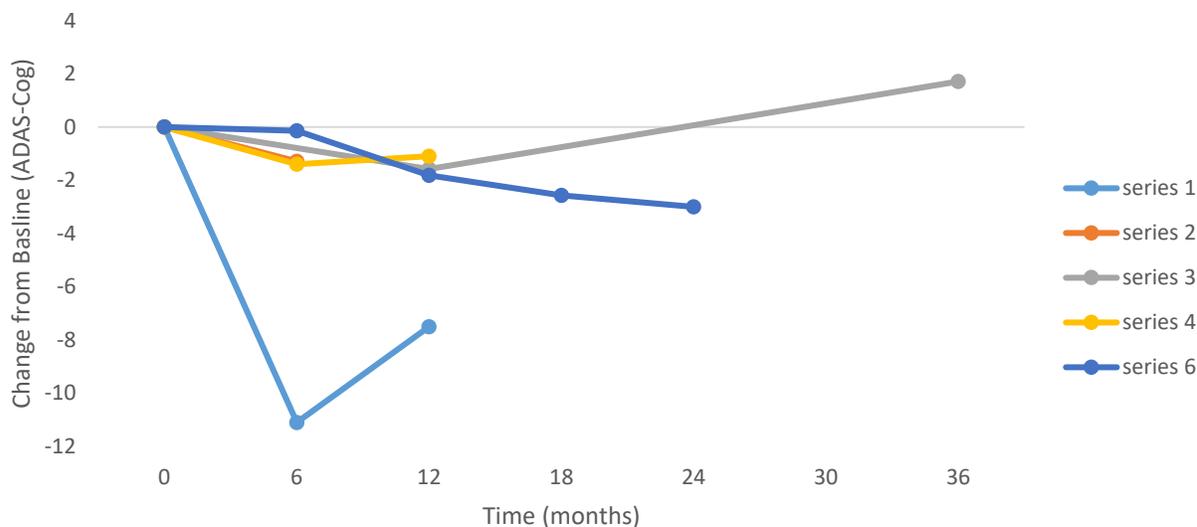


Figure 20: The change from baseline ADAS-Cog score was plotted against time in months for the rivastigmine treatments.

A decrease in MMSE scores from the start of treatment until 12 months is observed for tacrine. From 12 to 24 months no significant change is observed. 36 to 48 months showed large improvement until decline in scores was measured at 60 months. An initial increase in ADAS-Cog scores from the start of treatment until 24 months is observed. An improvement is then seen from 24 months until 36 months. No further ADAS-Cog scores were collected in this study. The

study has a relatively small sample size of $n=50$. However many data points were collected and the length of the study was the longest of all treatments and series. The data suggests that tacrine offered cognitive improvement after 36 months. More evidence is required to support this claim due to the limited available studies, and small sample size. Figures 21 and 22 show the change from baseline MMSE score against time and the change from baseline ADAS-Cog score against time, respectively, for the tacrine treatment trials.

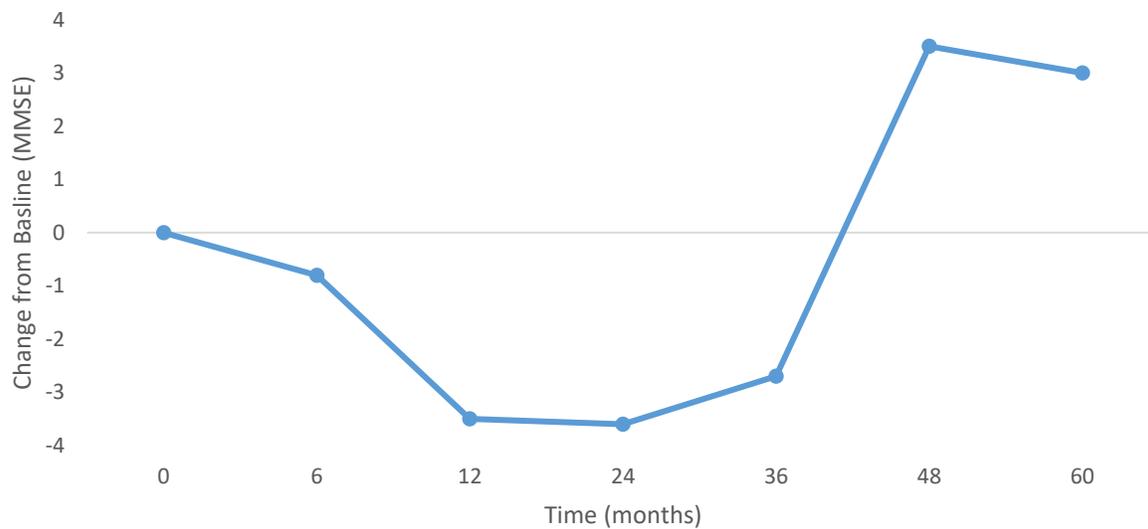


Figure 21: The change from baseline MMSE score was plotted against time in months for the tacrine treatments.

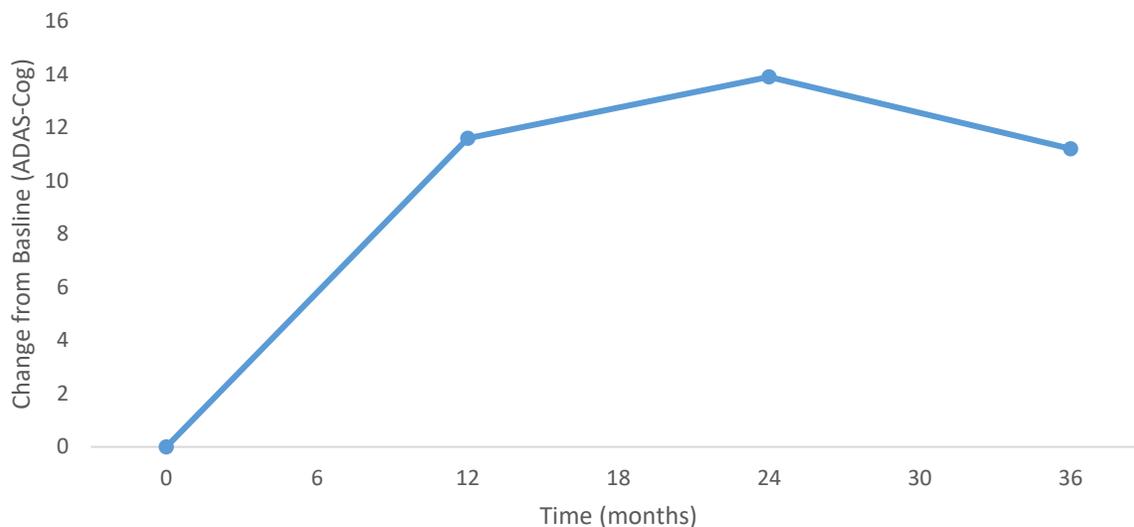


Figure 22: The change from baseline ADAS-Cog score was plotted against time in months for the tacrine treatments.

The KD treatment had the highest improvement of cognition per time according to MMSE scores and the second highest for ADAS-Cog scores. It is of importance to note the small study number (n=9), the short length of the study, and the presence of KD treatment in only one study. These limitations question the accuracy of these data and therefore results should be considered preliminary until more evidence is provided. The KD score change from baseline MMSE score against time and the change from baseline ADAS-Cog score against time are shown in Figures 23 and 24, respectively.

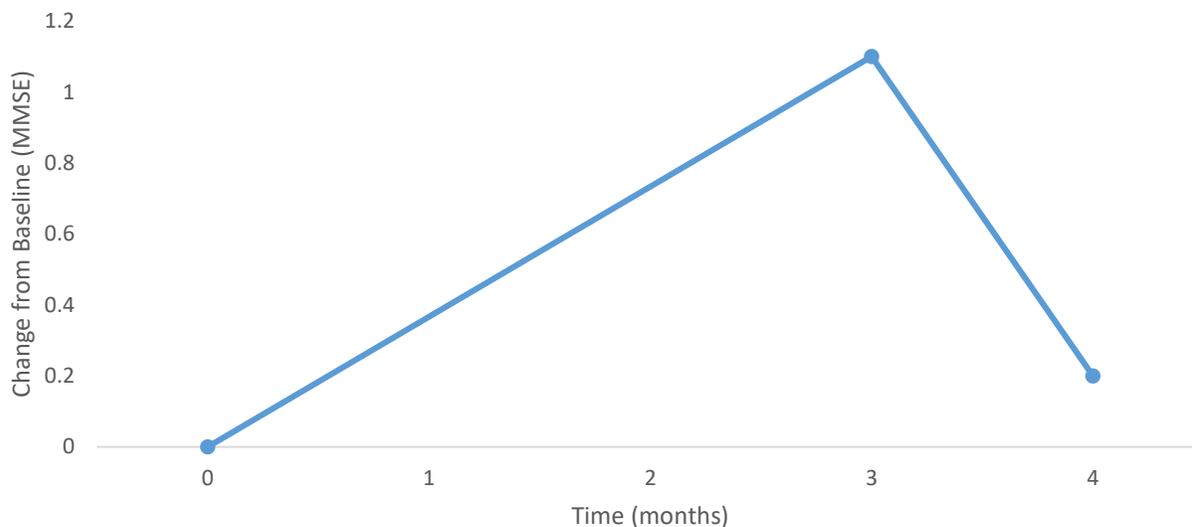


Figure 23: The change from baseline MMSE score was plotted against time in months for the KD treatments.

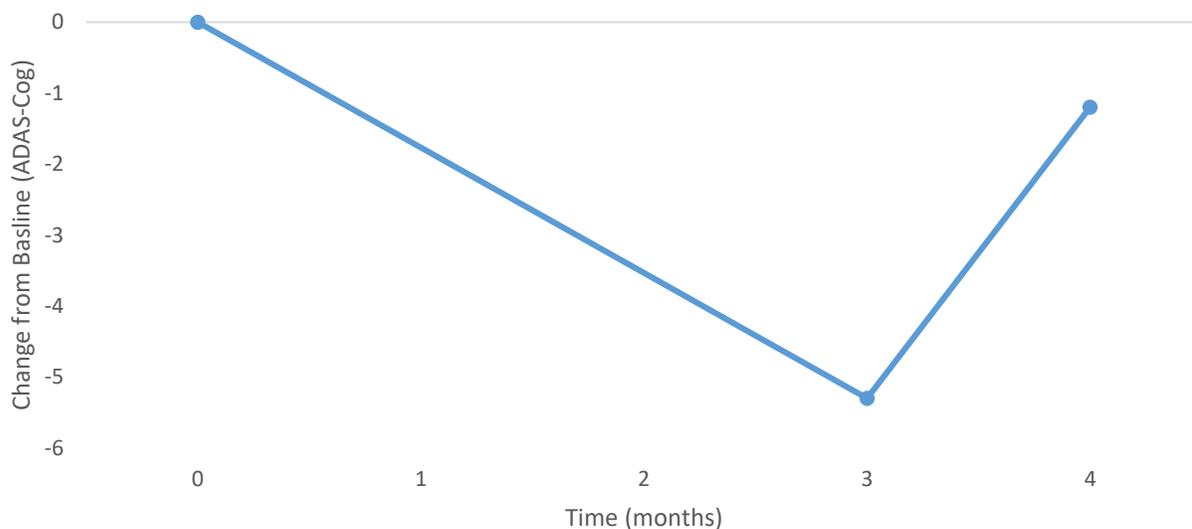


Figure 24: The change from baseline ADAS-Cog score was plotted against time in months for the KD treatments.

The average change in mean MMSE score per month was calculated for all treatment trials and series. For these calculations, washout period (when treatment was discontinued) data points were ignored. The average change in MMSE score per month show agreement with my previous observations for each treatment. The greatest average change in MMSE score per month was from KD treatment series 1, followed by galantamine treatment series 3 and

memantine treatment series 1 (both had the same calculated average), then donepezil treatment series 8, memantine treatment series 2, and donepezil treatment series 6. The high average for the KD treatment is expected due to the large measured improvement in MMSE scores over a short period of time. This does not take into account the long term effect of KD treatment on cognition, as more studies are necessary, but suggests preliminary results have a high efficacy.

The galantamine treatment series 3 initially showed improvement at 2, 6, and 12 months followed by an increasing decline in MMSE scores from 12 months until 24 months. The large sample size, and length of study support the accuracy of this data. The data in Figure 15 suggests that the benefit offered from galantamine is limited and questionable due to the decreasing improvement seen in series 3 and the continual decline in MMSE scores from series 1, and series 2. The high average for both memantine treatment series coincides with MMSE score improvement seen in Figures 7 and 17. Once again it is worth noting the small sample size and short length of the study. Similar to the KD treatment, memantine treatment offered a large improvement over a short period of time. However, more studies are necessary to support this conclusion, specifically longer studies with larger sample sizes. The donepezil treatments series 6 and 8 both showed high efficacy from the calculated average. However, Figures 3 and 13 only suggest improvement from series 6. Series 8 showed little improvement initially from the start of treatment until 6 months and decline until the end of study at 18 months. It is worthwhile to note that series 6 concluded at 6 months, the time that series 8 began to decline. Perhaps if series 6 had been extended further a similar trend may have been observed.

The large number of donepezil studies with varying outcomes suggest the perceived benefits should be approached cautiously. The average change for most donepezil treatment series were close to zero with series 1, series 6, and series 8 being exceptions. Series 1 had the

second largest decline of all treatment series for MMSE scores. The galantamine treatment series had the most widespread averages with series 1 having the third largest decline and series 3 having the second largest improvement. Series 2 had a small decline. It is worth noting that series 3 had the largest sample size of the galantamine treatment series, over four times larger than series 1. Both memantine treatment series showed positive scores but once again the small sample size questions the accuracy of these studies. Most of the rivastigmine treatment series showed minimal change from baseline except for series 5 which showed the fourth largest decline in average MMSE scores. Interestingly the tacrine treatment series, despite the long term improvement seen in Figures 11 and 21, had the largest average decline in MMSE scores. This is likely due to the decline in scores throughout most of the tacrine treatment study. These data are presented in Figure 25 and Table 1.

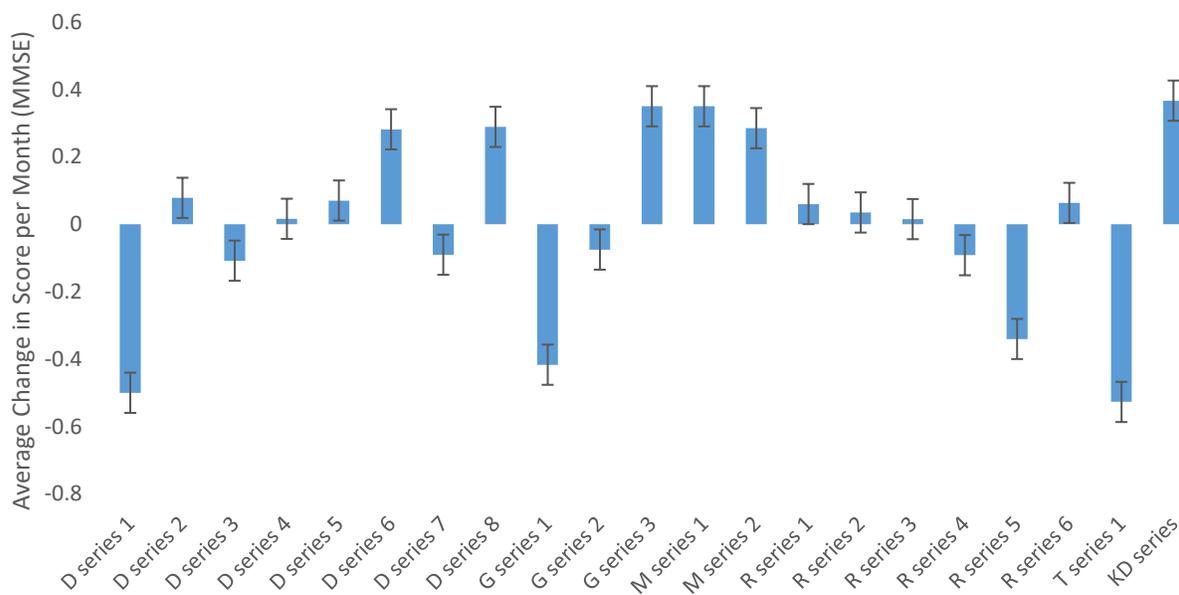


Figure 25: The calculated average change in MMSE score per month is shown for each treatment and series. Note that positive increases indicate an improvement in cognition.

Table 1: The treatment and corresponding series' calculated average change in MMSE score per month is shown. G represents galantamine, M represents memantine, T represents tacrine, R represents rivastigmine, and D represents donepezil.

<u>Treatment and Series</u>	<u>Average Change in MMSE Score per Month</u>
D series 1	-0.50
D series 2	0.078
D series 3	-0.11
D series 4	0.016
D series 5	0.070
D series 6	0.28
D series 7	-0.090
D series 8	0.29
G series 1	-0.42
G series 2	-0.075
G series 3	0.35
M series 1	0.35
M series 2	0.29
R series 1	0.060
R series 2	0.035
R series 3	0.015
R series 4	-0.091
R series 5	-0.34
R series 6	0.063
T series 1	-0.53
KD series	0.37

The greatest decrease in average change in ADAS-Cog score per month was rivastigmine treatment series 1, followed by KD treatment, then by memantine treatment series 2, donepezil treatment series 6, and then donepezil treatment series 5. The greatest increase in average change in ADAS-Cog score per month was tacrine treatment, donepezil treatment series 3, donepezil treatment series 8, and galantamine treatment series 3. Rivastigmine treatment series 1 had a decrease of scores at the 6 month measurement suggesting initial improvement. However, the scores increased at the 12 month measurement indicating limited efficacy with time. Series 3, series 4, and series 5 show a similar trend suggesting that improvement declines with time. Small average declines are seen in scores for all the other rivastigmine treatment series suggesting a trend of positive improvement of cognition via ADAS-Cog scores. However, this improvement

is small and the positive trend for all series is not consistent for rivastigmine treatment data in Figures 9, 10, 19, 20, and 25. This suggests that the trend is not indicative of high efficacy.

KD treatment saw an improvement in cognition which is consistent with the data presented in Figures 1, 2, 23, 24, and 25 suggesting high efficacy. The decrease in average change in ADAS-Cog score per month from memantine treatment series 2 is consistent with the data presented in Figures 7, 8, 17, 18, and 25 suggesting high efficacy. The donepezil treatment has the largest range in Figure 26. Series 6 showed the fourth largest decrease in scores and series 5 showed the fifth largest decrease in scores. Series 3 showed the second largest increase in scores and series 8 showed the third largest increase in scores. This coincides with the large variance of outcomes shown in Figures 3, 4, 13, 14, and 25 suggesting great inconsistency between studies and questionable efficacy. The galantamine treatment series showed high variability with series 3 showing an increasing average, series 2 showing a decreasing average, and series 1 showing very little change. These results conflict with the MMSE score averages in Figure 25. The data from Figures 5, 6, 15, and 16 suggest declines in cognition. Collectively the data from the galantamine treatment series are highly variable and suggests that the efficacy is questionable. The average change in ADAS-Cog mean score per month was calculated for all treatment trials and series (these calculations also excluded washout period data points) and are presented in Figure 26 and Table 2.

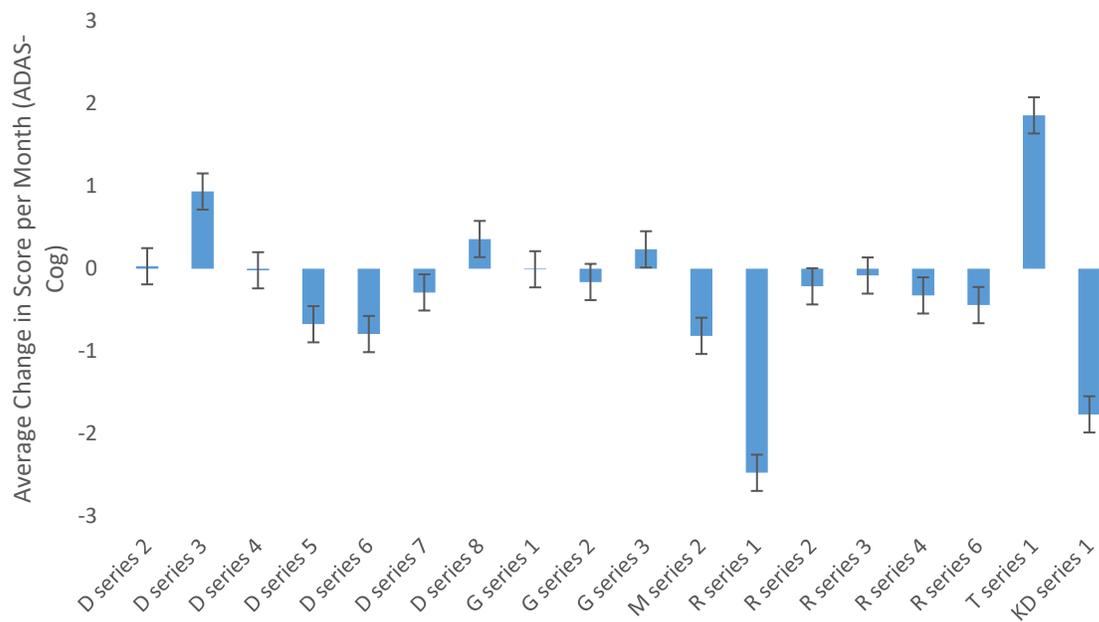


Figure 26: The calculated average change in ADAS-Cog score per month is shown for each treatment and series. Note that negative increases indicate an improvement in cognition.

Table 2: The treatment and corresponding series' calculated average change in ADAS-Cog score per month is shown. G represents galantamine, M represents memantine, T represents tacrine, R represents rivastigmine, and D represents donepezil.

<u>Treatment and Series</u>	<u>Average Change in ADAS-Cog Score per Month</u>
D series 2	0.028
D series 3	0.93
D series 4	-0.021
D series 5	-0.67
D series 6	-0.79
D series 7	-0.29
D series 8	0.36
G series 1	-0.0083
G series 2	-0.16
G series 3	0.23
M series 2	-0.82
R series 1	-2.48
R series 2	-0.22
R series 3	-0.084
R series 4	-0.33
R series 6	-0.44
T series 1	1.9
KD series 1	-1.8

Conclusion

Overall the greatest increases in cognition come from KD treatment and memantine treatment as evidenced by both MMSE and ADAS-Cog score changes. This suggests that these two interventions hold the highest efficacy. This is especially interesting because these two treatments are not acetylcholinesterase inhibitors like the rest of the treatments. It is worth noting that the KD study had the lowest sample size and the shortest study length. It is also worth noting that memantine studies also had low sample sizes and short studies. These factors make the accuracy of the presented data questionable and therefore these results should be considered preliminary, requiring more evidence to confirm or deny these claims.

Donepezil treatment and galantamine treatment both showed high variability and inconsistency between studies. The heavy inconsistencies between individual series of the same treatment and differences in MMSE and ADAS-Cog scores of the same series question the efficacy of the treatments. The limited number of studies may account for some of these inconsistencies which could result from an insufficient amount of data. The rivastigmine treatment showed small benefits from decreases in ADAS-Cog scores but large declines in MMSE scores. The largest rivastigmine treatment series (and largest of all treatment series) had $n=2010$ and showed a large decrease in MMSE scores. This study did not measure ADAS-Cog scores but the large sample size, length of the study, and consistent decreases in cognition shown by other rivastigmine series suggests that this treatment does not have high efficacy. The tacrine treatment study showed short term cognitive decline but long term improvement. This may suggest this treatment has efficacy in the long term. However the relatively small sample size from the single tacrine study is not sufficient evidence to support this conclusion. More studies are necessary to analyze the efficacy of tacrine treatment but currently the data suggests this treatment does not have high efficacy.

These results potentially suggest that acetylcholinesterase inhibitors have limited efficacy and that alternative treatments for AD should be explored in the future. A more in depth study of the data available could be performed by retrieving the raw data from each of these individual studies and performing statistical analysis. There are several issues with this approach including privacy of data, the time period since publication of studies, and time required to analyze the data. Limitations of this study include the inability to statistically analyze available data, limited number of available studies, and inconsistencies between certain treatments. This research explores a spectrum of treatments currently used for the treatment of AD and their

efficacy. The presented research also highlights the need for future work in order to identify practical methods for the inclusion of KD into patient-centered care.

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