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A RETROSPECTIVE MEDICATION CHART REVIEW OF PATIETS CLINICALLY DIAGONSED WITH ALZHEIMER'S DISEASE, VASCULAR DEMENTIA AND MILD COGNITIVE IMPAIRMENT

THESIS

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By

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Sandra Longoria

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CHAPTER I

INTRODUCTION

In partial fulfillment of curriculum requirement for Masters of Clinical Research management, I completed a six month internship at the Department of Internal Medicine, Division of Geriatrics at the University of North Texas Health Science Center (UNTHSC). I was under supervision of two on- site mentors, principal investigator Dr. Janice A. Knebl D.O., M.B.A. and research coordinator Barbara Harty, R.N., M.S.N, G.N.P. The duties I performed included assisting the clinical research coordinator with data entry, lab processing, safety reports and follow-ups. During my internship I focused on the management of two ongoing clinical trials. The first trial is a Phase-3, multicenter, randomized, double blind, placebo controlled, parallel group, efficacy and safety trial of Bapineuzumab in patients with mild to moderate Alzheimer disease (AD) who are Apolipoprotein E4 (ApoE4) carriers and non carriers. The aim is to enroll a total of fourteen subjects into this study. The subjects are divided into two separate categories: ApoE4 carriers and non carriers. The groups are randomized and will receive infusion of the study drug, babpineuzumab, or a sodium chloride placebo. This clinical trial will provide insight to the progression of AD, the effects dementia has on family members, any safety implications the study drug may cause and, most importantly, whether the study group has the potential to modify the disease state of AD and dementia.

The second clinical trial I assisted is entitled “Inverse Association Between Alzheimer’s Disease and Caner: A Mitochondrial Estrogen Receptor beta Paradigm.” During this trial, blood samples are collected from subjects who have AD and control subjects. The blood will be sent off for study evaluation and analysis of whether a correlation between AD and cancer exists. I assisted in subject screening and recruitment from the patient population of the UNTHSC Internal Medicine Geriatrics Clinic, Clinical Research Subjects or Texas Alzheimer’s Research Consortium (TARC).

BACKGROUND

A. Alzheimer's Disease

Alzheimer's disease (AD) is a rapidly growing neurodegenerative disease which currently affects more than five million people of the United States population (www.alz.org). An estimated 4.6 million cases are added worldwide every year (Yarti and Corey-Bloom, 2007). AD counts for 60% of the most common forms of dementia (www.alz.org). In 2009, it was reported by the Alzheimer's Association that every 70 seconds, someone is diagnosed with AD. It is also the 6th leading cause of death in the United States (www.alz.org). People who are diagnosed with AD typically suffer or will have trouble with speech or comprehension of spoken or written language (www.alz.org). They will usually have difficulty recognizing or "finding a name" for objects such as pen or watch and demonstrate trouble signs of executing motor activities such as knowing how to feed (www.alz.org). Other signs of AD include mood/behavior changes, disorientation and confusion. Overall the decline in memory and/or cognitive function affects day-to-day living. AD is observed in people of 65 years of age and older, however there a very few cases revealing individuals as young as 30 years of age to have AD (www.alz.org). Strong evidence suggests that AD can vary with gender, race and ethnicity; however, there is not any consistent data available (www.alz.org). In 2008, it was reported that 2.4 million women over the age of 71 had dementia versus the 1 million men also aged 71 and above (www.alz.org). The increasing number of women with AD

over men can be explained by the simple fact that women live longer lives than do men (Plassman et al., 2007). With regards to race and ethnicity, research shows that Africans Americans are more likely to develop AD compared to Caucasian Americans, but the higher incidence does not reflect any significance (Plassman et al., 2007). In Texas alone, it is estimated than 201,000 to 499,100 individuals suffer from AD (www.alz.org).

The most common hallmark that contributes to the pathology of AD is the presence of beta amyloid (Aβ) plaques, specifically $A\beta_{1-42}$ or $A\beta_{1-40}$, and neurofibrillary tangles compromised of hyperphosphorylated tau proteins that aggregate in certain regions of the brain responsible for cognitive impairment and memory (Selkoe, 2002). The process of Aβ plaques begins when the Aβ peptide is created by a two step proteolytic cleavage of the amyloid precursor protein (APP) by beta- (β) and gamma- (ɣ) secretases (Parameshwaran et al., 2007). It is specific ɣ-secretases cleavage activity that creates $A\beta_{1-42}$ in the endoplasmic reticulum and $A\beta 1_{-40}$ in the trans-golgi regions of the cell (Parameshwaran et al., 2007). The presence of Aβ plaques are known to contribute to oxidative damage leading to neuronal impairment (Yatin et al., 1999). Formation of Aβ plaques is not the only hypothesis of AD under observation. Researchers have discovered that AD and other forms dementia may be due to of synaptic processes in which synaptic loss or synaptic dysfunction occurs years prior to neuronal failure (Parameshwaran et al., 2007). Loss of function of the synapse leads to imperfect neurotransmission. This evidence is seen in transgenic mice over expressing APP (Larson et al., 1999). Furthermore, other research suggests that cholinergic and glutamatergic excitatory

neurotransmitter system dysregulation leads to overall synaptic dysfunction and eventually neurodegeneration in AD (Parameshwaran et al., 2007).

B. Vascular Dementia

Vascular dementia (VaD) is the second most common form of dementia that also occurs to in the elderly who are 65 years of age and older (www.alz.org). In most cases, VaD usually occurs after a person undergoes a stroke in which the blood flow is disrupted in the brain, thus, depriving cells of food and oxygen (www.alz.org). People who suffer from VaD often exhibit physical dysfunction with minimal or non-existent memory loss (Roman, 2003). VaD patients also exhibit AD characteristics such as cognitive decline, decreased functional ability and even behavioral modifications (Small, 2001). Often AD and VaD coexist in a mixed-state form of dementia (Gorelick et al., 1996). AD and VaD risks both increase with age and have similar overlaps in symptoms, pathology and mortality (Kalaria, 1999). The elderly are at significant risk for any type of vascular events. Risk factors include hypertension, coronary artery disease, atherosclerosis, diabetes, and smoking (Kalaria, 1999). Patients who have VaD have significant increase in difficulty in functions that need attention, planning, and thought process (Erkinjuntti, 2001). Furthermore, mood or personality changes such as becoming anxious or depressed, often occur earlier and more severe with patients who suffer from VaD (Hargrave et al., 2001). VaD has also been associated with a decrease in function of cholinergic activity and protein aggregates in the brain (Kalaria, 1999). Other hallmark features include micro-infarction and white matter collection in the brain.

C. Mild Cognitive Impairment

Mild cognitive impairment (MCI) is described as an individual having difficulty with language, memory and cognitive function that is easily noticeable. Up to 20 percent of people 65 and over have MCI (www.alz.org). A person with MCI is most likely to fully develop AD (www.alz.org). The development of MCI seems to be that of normal age related cognitive decline. Overall, MCI individuals experience forgetfulness but seem to function well overall (www.alz.org). If a person exhibits frequent abnormal memory conflicts, such as forgetting recent or significant events, then a mental evaluation is warranted. A mental status examination (MSE) can be performed by a physician to access whether MCI is present. Magnetic resonance imaging (MRI) scans of the brain, thyroid abnormalities, and vitamin B12 deficiency and conclude reasoning for cognitive impairment can also predict MCI (www.alz.org). A person with MCI typically deals with daily activities with ease. Symptoms usually become apparent when their memory is stressed or an activity requires the ability to multi-task (www.alz.org). MCI, characteristically, is a normal part of aging and it has been recently noted as a valuable and recognizable risk factor for AD (Peterson, 2004). Rarely is MCI diagnosed; only when signs and symptoms have become apparent is it finally recognized.

D. Apolipoprotein E genotype

Apolipoprotein E (ApoE) is a specific type of apoprotein that is necessary for the breakdown of triglyceride-rich particles (Gunzburg, 2009). ApoE plays an important role in lipoprotein metabolism and the development of cardiovascular disease. Specifically, ApoE allele ε4 (ApoE4) has been shown to be associated with AD and reduced cognition (Davigon et al., 1988). Interestingly, research has shown that the ApoE4 genotype seems to predict the rate of cognitive decline in AD in a dose-dependent and age-dependent manner (Martins et al., 2005). VaD may also be influenced by ApoE4 (Kalaria, 1997). Research has shown that carriers of the ApoE4 allele have a three-fold greater risk for AD and cardiovascular disease in comparison to non-carriers (Kalaria, 1997).

E. Acetylcholinesterase Inhibitors for Treatment of Dementia

Aricept©, Razadyne ER©, and Exelon© are the three most prescribed acetylcholinesterase inhibitors (AChEIs) to reduce the progression of dementia (Ellis, 2005). Cholinesterase inhibitors work by blocking the hydrolysis activity of specific neurotransmitter, acetylcholine (ACh). ACh is vast neurotransmitter that plays an extensive role in the peripheral nervous system by stimulating muscle action as well as the central nervous system causing excitatory actions in neurons. It has further involvement in the autonomic nervous system and is exclusive to the somatic nervous system. Maintaining homeostasis of ACh is essential for normal function of the body.

Recent research has shown a relationship between decreased levels of the acetycholine neurotransmitter and its contribution to learning and memory loss (www.nih.gov). AChEIs work by inhibiting the acetylcholinesterase enzyme, which is responsible for the chemical breakdown of acetylcholine (www.nih.gov). The overall effect is slower degradation of acetylcholine and increased cholinergic activity in the brain (www.namenda.gov).

F. Glutamate as a Target Therapeutic for Dementia

Glutamate is another neurotransmitter in the brain that helps facilitate the learning and memory process. Glutamate is a chemical messenger which transmits messages from one target cell to another upon binding and activation of metabotropic glutamate receptors (mGluR). mGluR belong to specific class of g-protein-linked receptors are divided into three groups. Group I mGluR activity is coupled to intracellular calcium movement (Conn and Pinn, 1997). Group II and III mGluR act as presynaptic autoreceptors (Shigemoto et al., 1997). Glutamate release is controlled by mGluR located in the presynaptic cleft and, therefore, optimizes glutamate transmission at the synapse (Continho and Knopfel, 2002). Changes or abnormal activity in glutamate has been shown to be a factor in AD (www.namenda.com). Most particularly, glutamate activity has shown to be significantly decreased by Aβ (Parameshwaran, 2007). Nameda® is the only drug type available which targets glutamate activity (www.nameda.com). Namenda® can be taken and is most often prescribed concomitant with other AD medications such as Aricept®. Namenda® mechanism of action is to act as an antagonist

to the N-methyl d-aspartate (NMDA) receptor, thus increasing glutamate activity. In addition, Namenda®, has been shown to significantly increase the ability of an AD patient to perform daily activities (www.namenda.com).

G. General Drug Therapeutics and Classification

Cholesterol Reducing Medication

Statin drugs are considered one of the most frequent prescribed medications used for the reduction of elevated plasma cholesterol levels, or hypercholemia. Branded statin drugs include Crestor®, Lipitor®, Zocor®, Mevacor®, Pravacol®, and Lescol®. They work effectively by stabilizing the inhibition of 3-hydroxy-3-methylglutarul-coenzyme A (HMG-CoA), a key factor in cholesterol synthesis in the liver (Srancu & Sima, 2001). Cholesterol synthesis produces both "good" high density lipoproteins (HDL) and "bad" low density lipoprotein (LDL). HMG-CoA reductase inhibitors involve the interruption of LDL synthesis, degradation, secretion, oxidation and scavenger receptor expression (Bellosta et al., 2000). Overall, the general mechanism of action of statin drugs is to decrease the level of saturated "bad" LDL in the blood and increase the level of "good" HDL. Good cholesterol, or HDL, is essential for development of the outer coating of cells (cell membrane), synthesis of bile acids to digest foods, and hormone production (www.health.havard.edu). Most statin drugs are obtained from fungal fermentation (Srancu & Sima, 2001). Stain drugs are well tolerated within the body; however, limited adverse effects on liver and muscle toxicity have been reported (Srancu & Sima, 2001). They are effective in reducing LDL levels and even lowering plasma triglycerides in

hypertriglyceridemic patients (Srancu & Sima, 2001). In addition, statin drugs have shown to significantly reduce the incidence of coronary adverse events (Srancu & Sima, 2001). Research has also shown that statin drugs can also inhibit tumor growth (Srancu & Sima, 2001).

Anti-Hypertensive Drugs:

Blood pressure is developed by the contraction of the heart to pump blood from the heart through the body's blood vessels. Uncontrolled blood pressure can lead to feeling dizzy, frequent headaches and nosebleeds. These symptoms can become life-threatening if not controlled properly by causing damage to your arteries (atherosclerosis), aneurysms, heart failure, kidney malfunction, vision loss, and even trouble with memory and comprehension (www.mayoclinic.com). Research has shown that a relationship exists between hypertension and cognitive impairment (Starr et al., 1993). Anti-hypertensive drugs work to lower the body's blood pressure. There are several classes of anti-hypertensive medications. Thiazide diuretics, such as Lozol®, work by stimulating the kidneys to eliminate sodium and water, thus, reducing total blood volume (www.mayoclinic.com). Beta blockers cause the heart to beat a bit slower and with less force therefore lowering overall blood pressure (www.mayoclinic.com). Angiotensin-converting enzyme (ACE) inhibitors serve as a vasodilator by blocking the enzyme, which leads to the conversion of angiotensinogen to angiotensin and causes blood vessels to narrow (www.mayoclinic.com). One other class of anti-hypertensive drugs is calcium channel blockers (CCB), which also work by relaxing the blood vessels and slow down your heart rate (www.mayoclinic.com). High blood pressure typically develops over time

and will typically affect 1 in 3 adults in the United States (www.nhlbi.nih.gov). Other risk factors for developing hypertension include age, race/ethnicity, weight, gender, and unhealthy lifestyle habits. African-Americans and Hispanics are more likely to develop high blood pressure as opposed to Caucasian (www.nhlbi.nih.gov).

Mood/Personality Medicine: Anti-Depressants and Anti-anxiety Medication

Mood and personality changes often occur as dementia progresses (www.alz.org). Medications such as anti-depressants help improve a person's well-being. There are three major classes of anti-depressants categorized by function: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs) (Lenox & Frazer, 2000). Serotonin and norepinephrine are neurotranmsitters of the brain that are responsible for mood. MOAIs allow for abundance of the neurotransmitters to be readily available by inhibiting the enzyme responsible for their degradation (Lenox & Frazer, 2000). TCAs work by blocking the neurons ability to reabsorb the neurotransmitters, also leaving a greater amount of chemical for mechanistic action (Schimelpfening, 2006). SSRIs work very similar to TCAs but are selective to serotonin only (Schimelpfening, 2006).

Prevention of Vascular Disease with Anti-coagulants

Anti-coagulant medication, such as Coumadin®, help prevent coagulation (clotting) of the blood. This medication is widely prescribed to patients for prevention or rehabilitation of a blood flow obstruction to the brain such as a stroke. Approximately 1/3 of the population in the United States takes an 81mg aspirin tablet daily to prevent the

risk of strokes and heart attacks (Cooney, 2009). Plavix® is particular type of the anti-coagulant in which helps prevents platelet aggregation in the arterioles thus reducing clot formation and subsequently lowers the risk of heart attacks and strokes (www.plavix.com). Plavix® works by inhibiting adenosine diphosphate (ADP) induced platelet aggregation (www.plavix.com). Anti-platelet medications are extremely effective in improving arterial circulation (www.plavix.com). They have been known to help aid the areas of platelet aggregation that anti-coagulants have little effect on. Together the use of anti-coagulants significantly reduces cardiovascular risk.

Anti-Oxidant (Vitamins):

Oxidative stress is a process in which there is an abundant formation of free radicals that can produce detrimental damage to neurons and therefore contribute to the pathogenesis of dementia. Anti-oxidants can counteract this process, thus protecting neurons. Vitamin E has been studied as a possible therapy for AD because of its potent antioxidant properties (Hogan et al., 2008). In a recent study, a MMSE was given to patients with mild to moderate AD after 230 days of treatment with Vitamin E (Sano et al., 1997). There was a significant increase in scores, thus showing improvement on cognition (Sano et al., 1997). However, a study involving the use of Vitamin E with MCI subjects showed no improvement at all (Petersen et al., 2005). Ginkgo biloba is another anti-oxidant which has shown beneficial action in patients with dementia by promoting vasodilatation, reduced blood viscosity, reduced free radicals and modification of neurotransmitter release (Briks et al., 2002). Ginkgo is also used frequently to improve memory. Ginkgo has been thoroughly studied in clinical trials and has shown to have both a positive effect

(Kanowski et al., 2003) and also no significant effect (Van Donigen et al., 2003) on cognition. Futhermore, Vitamins B6 and B12 along with Folic acid have also been studied for the treatment and prevention of cognitive decline. Unfortunately, these vitamins produced no evidence of treatment effect (Hogan et al., 2008). The use of antioxidant therapy for the treatment of cognition decline is widely accepted for the decrease of free radicals, however, there still insufficient data to recommend for the use and treatment of dementia related diseases.

CHAPTER II

HYPOTHESIS, SPECIFIC AIMS AND METHODS

Hypothesis:

Currently there is no cure for any form of dementia. However, some pharmaceutical companies have successfully produced effective medication to help slow the progression of the rapidly growing disease. For my practicum report, I will address the issue whether medicinal treatment varies significantly among AD, VaD and MCI patients. This will provide powerful insight regarding dementia, current treatment options and determine whether medicinal trends may exists.

Specific Aims and Methods:

Specific Aim 1: Accessibility of AD, VaD and MCI patients

The first aim of this practicum is to obtain individuals who are clinically diagnosed with AD, VaD and MCI. Their disease state will be validated based on past history such as completion Mini-Mental State Examination (MMSE), history of strokes or any other blood flow obstructions, and by doctor referral. Data such as sex, age and medication history will be recorded. Twenty-five (25) subjects from the UNTHSC Patient Care Center Division of Internal Medicine with each form of dementia (AD, VaD, MCI) were examined.

Specific Aim 2: Drug comparison between AD, VaD and MCI patients.

The second aim of this practicum is to conduct a retrospective chart review of each subject. Any medicinal history will be recorded and categorized into the major pharmaceutical drug classes. Graphs will be composed to illustrate trends between each of the mentioned forms of dementia.

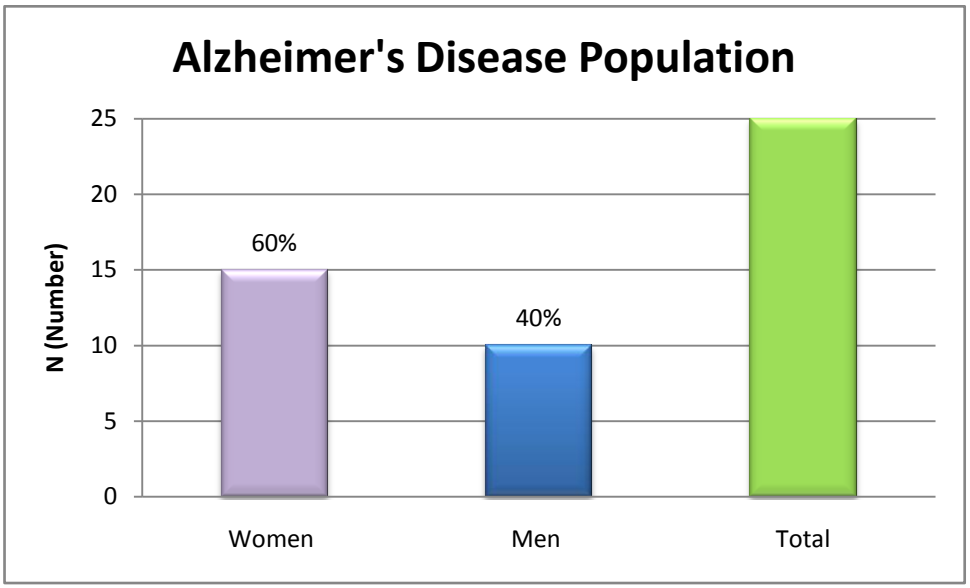
CHAPTER III

RESULTS

Specific Aim 1: Accessibility of AD, VaD and MCI patients

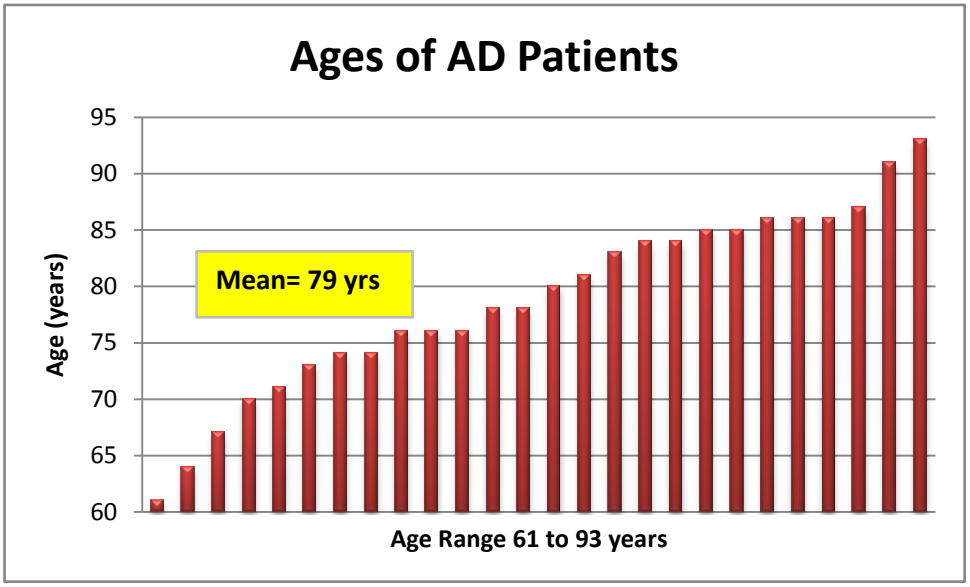
Patient charts were obtained from UNTHSC Patient Care Center Internal Medicine Department of Geriatrics and reviewed. AD sample population was generated by doctor referral. During the respective chart review, the diagnosis of AD was confirmed by diagnosis codes. A total of twenty-five (25) patient charts were reviewed. Figure 1 demonstrates the gender of the subject population. There were 15 women (60%) and 10 Men (40%).

Figure. 1: Alzheimer's disease Sample Gender



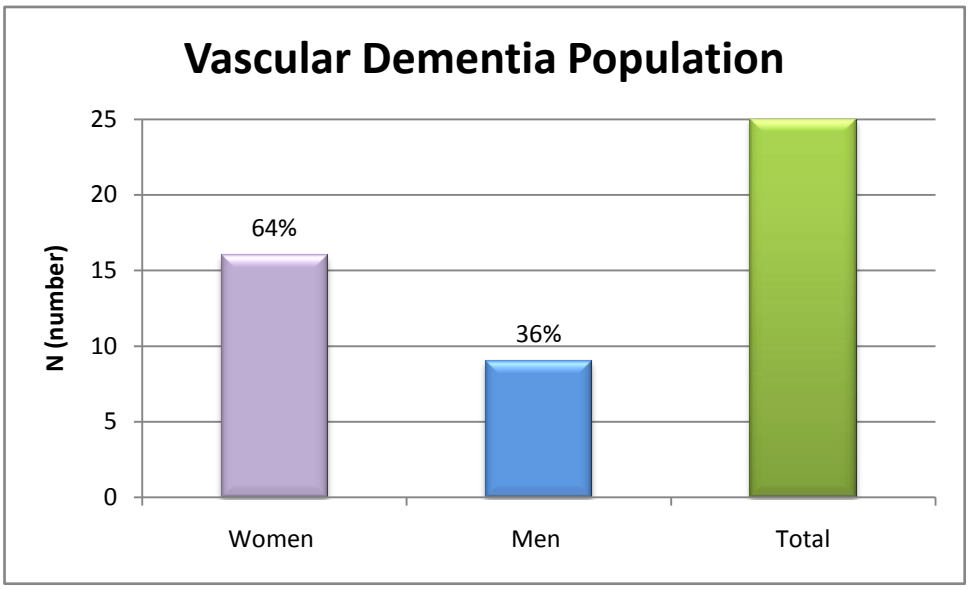
Sample population age was also recorded during the respective chart review. The age range of both men and women was 61 to 93 years of age. The average age of AD patients was 79 years. Figure 2 is a graphical representation of the ages of the twenty-five patients.

Figure: 2: Age Range of AD Sample Population



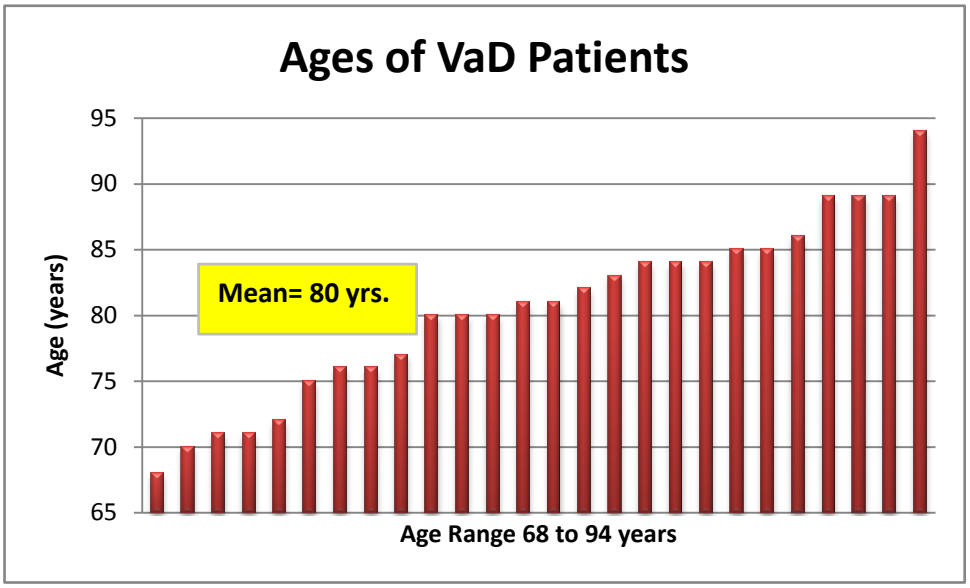
Charts of patients with VaD were reviewed. The VaD sample population was generated by doctor referral. During the respective chart review, diagnosis of VaD was confirmed by specific diagnosis codes. A total of twenty-five patient charts were reviewed. Figure 3 demonstrates the subject population within the sample size as 16 women (64%) and 9 men (36%).

Figure 3: Vascular Dementia Sample Population



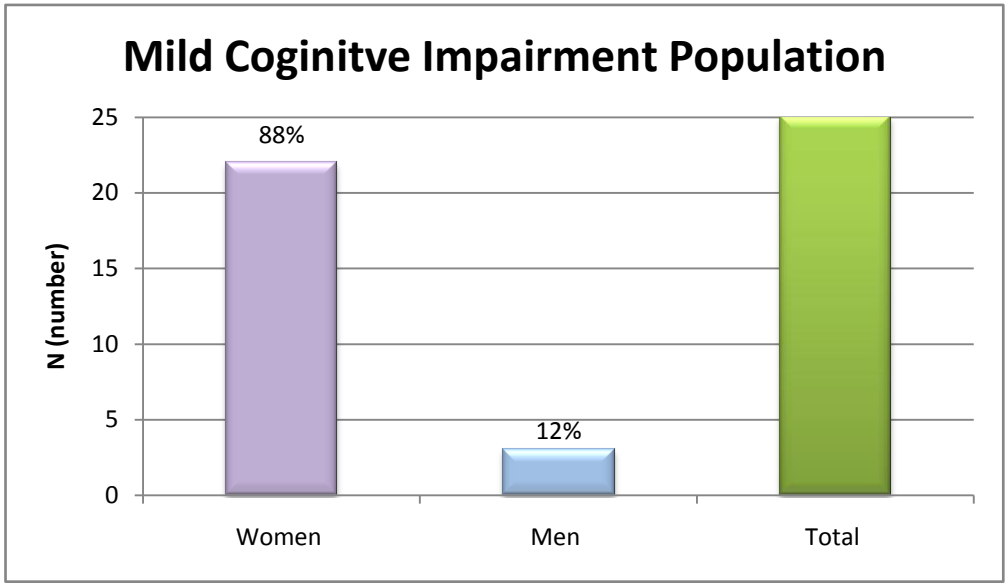
Sample population age was also recorded during the respected chart review. The age range of both men and women was 68 to 94 years of age. The average age of VaD patients was 80 years. Figure 4 is a graphical representation of the age group.

Figure 4: Age Range of VaD Sample Population



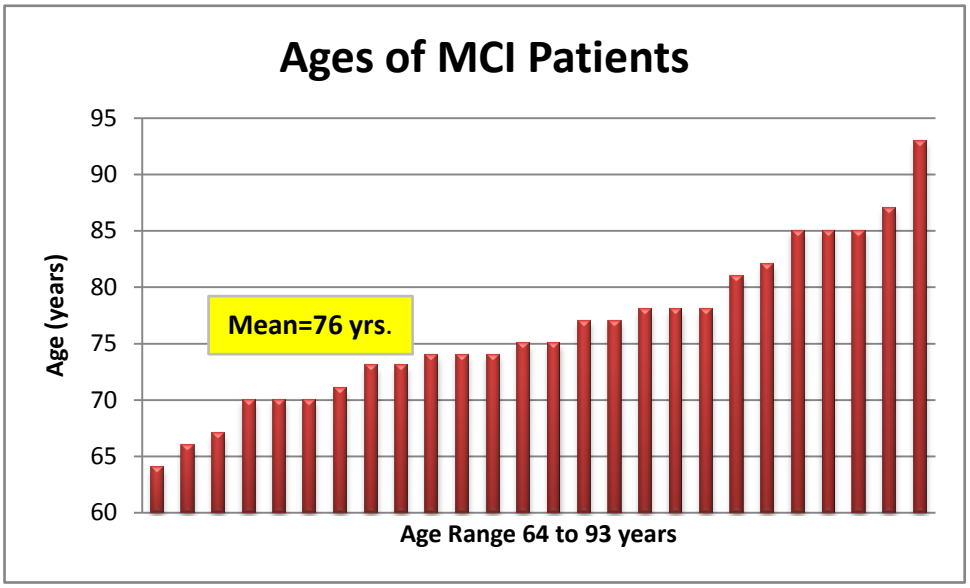
Patients were charts were reviewed from UNTHSC Patient Care Center Internal Medicine Department of Geriatrics. MCI sample population was generated by doctor referral. During the respective chart review, diagnosis of MCI was confirmed. A total of twenty-five patient charts were reviewed. Figure 5 demonstrates the subject population within the sample size as 22 women (88%) and 3 men (12%).

Figure 5: Mild Cognitive Impairment Sample Population



Sample population age was also recorded during the respected chart review. The age range of both men and women was 64 to 93 years of age. The average age of MCI patients was 76 years. Figure 6 is a graphical representation of the age group.

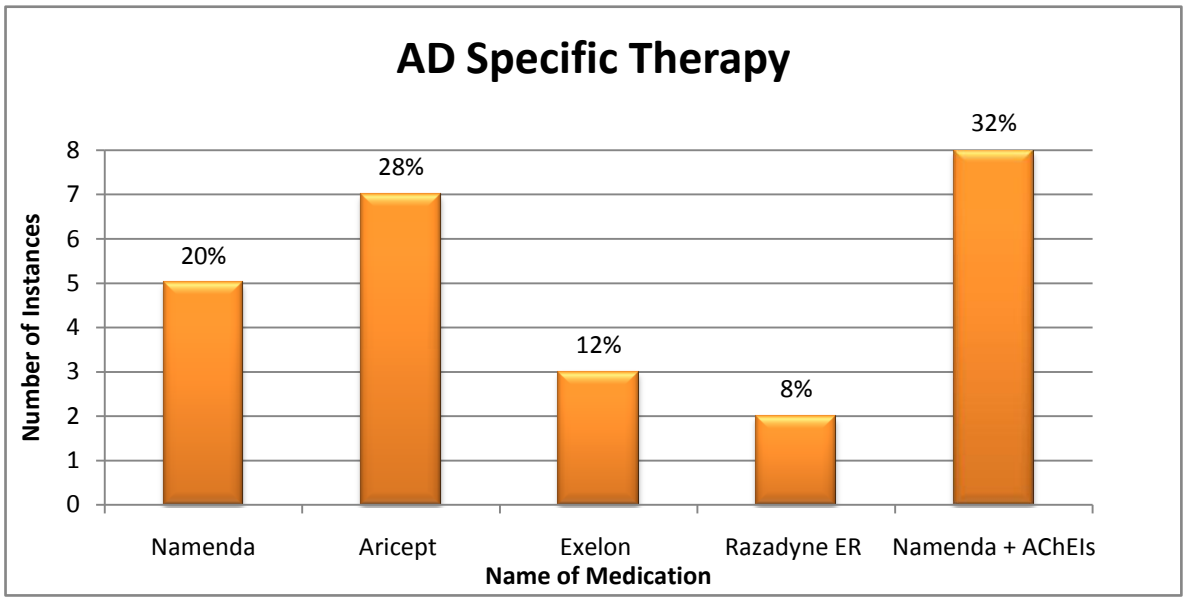
Figure 6: Age Range of MCI Sample Population



Specific Aim 2: Drug comparison between AD, VaD and MCI patients

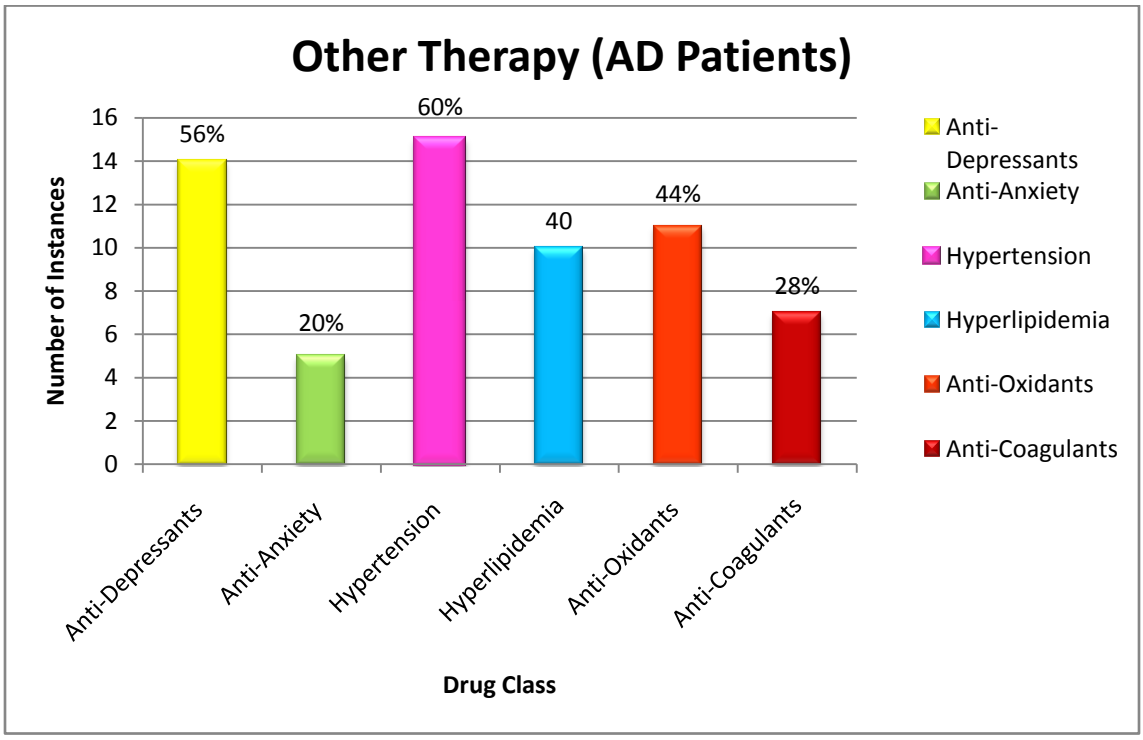
The retrospective chart review included the documentation of AD specific therapy on AD patients. As a result, 5 subjects were taking Namenda®, 7 subjects Aricept®, 3 subjects Exelon® and 2 subjects Razadyne ER®. At least 8 subjects were reported to use both Namenda and another form of AChEIs. Aricept seems to have a 20% treatment lead over other AChEIs used. Combination therapy of both Namenda plus a AChEIs also shows striking popularity and preferential treatment of AD. Figure 7 summarizes these treatment regimens in the twenty-five AD subjects.

Figure 7: Use of Specific AD Therapy within the AD Population



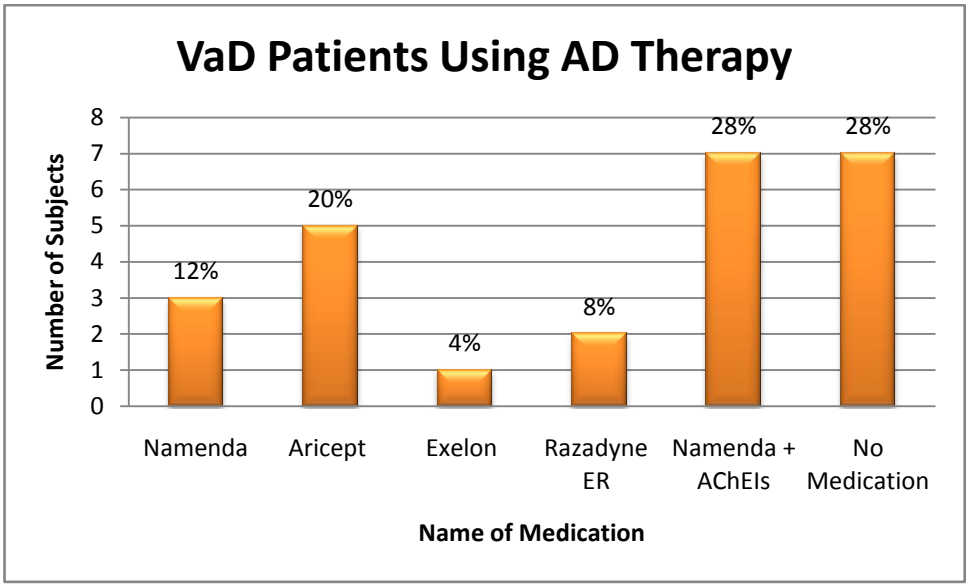
The retrospective chart review also documented other drug therapies commonly prescribed to AD patients. Data indicates that 14 subjects (56%) use anti-depressant medication, and 5 subjects (20%) use anti-anxiety medication. Surprisingly, 15 subjects (60%) reported the use of hypertension medication and 10 subjects (40%) use medication for hypercholemia. The reported use of anti-oxidant medication in AD patients was 11 subjects (44%). There were 7 subjects (28%) with documented use of anti-coagulants within AD sample database. Only one subject was using an anti-platelet medication. Figure 8 is a graphical representation of the use of other therapeutic medicine within the AD patients population.

Figure 8: Use of Other Therapeutic Medicine within the AD Population



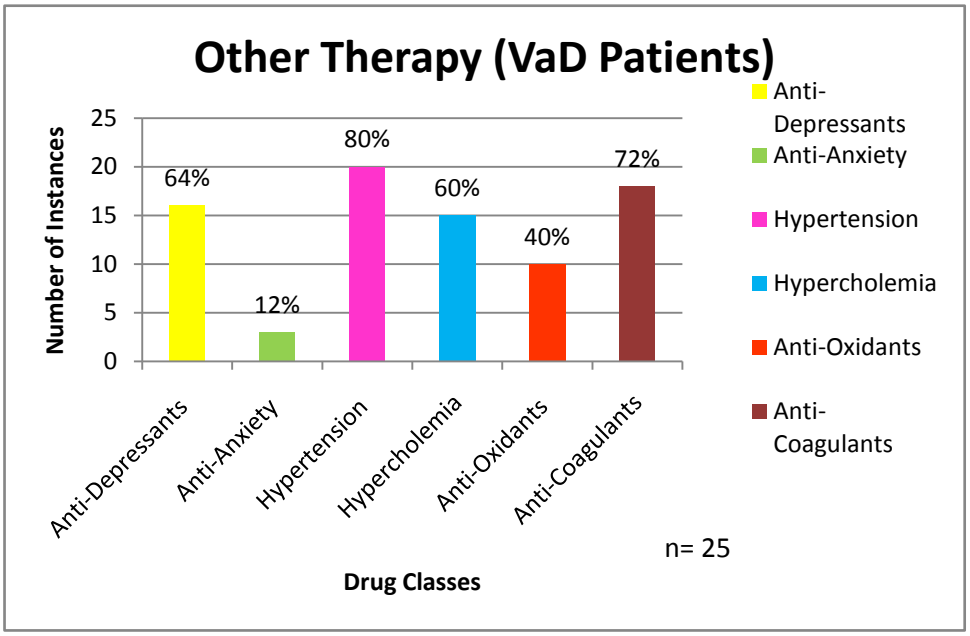
The retrospective chart review included the documentation of AD specific therapy on VaD patients. As a result, 3 subjects were on Namenda®, 5 subjects on Aricept®, 1 subjects on Exelon® and 2 subjects on Razadyne ER®. At least 7 subjects were reported to use both Namenda and another form of AChEIs. Combination therapy of both Namenda plus an AChEIs also shows popularity and preferential treatment to slow the progression of VaD related complications. However, 7 subjects (28%) do not use AD specific medication. Figure 9 is a graphical demonstration of the fore mentioned results.

Figure 9: Use of Specific AD Therapy Medicine within the VaD Sample Population



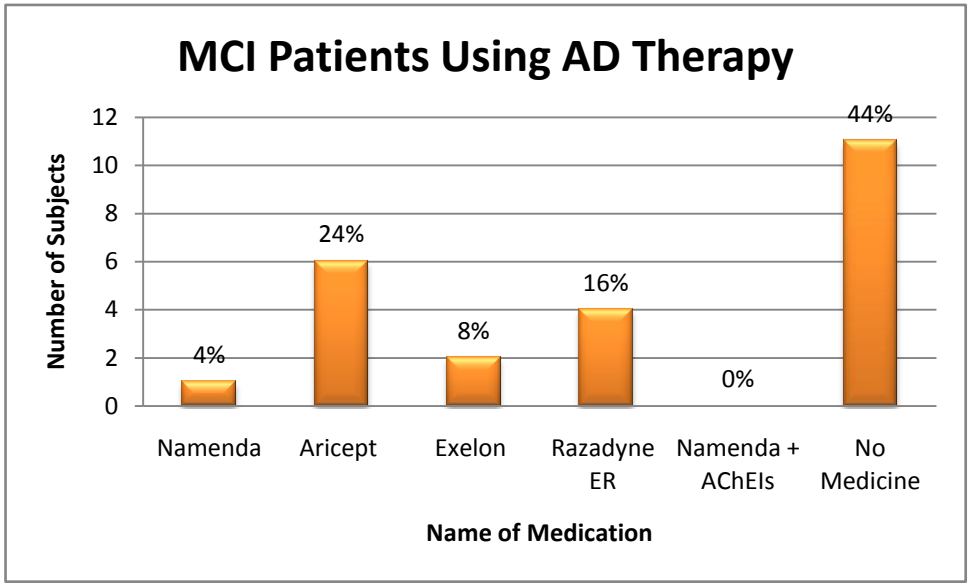
The retrospective chart review also included the documentation of other drug therapy commonly prescribed to VaD patients. As a result it was shown that 16 subjects (64%) uses anti-depressants medication. The use of anti-anxiety medication was 3 subjects (12%). In addition, 20 (80%) of the VaD subjects reported the use of hypertension medication and 15 subjects (60%) showed use of hypercholemia medication. In addition, 10 subjects or 40% reported the use of anti-oxidants. There were 18 VaD subjects (72%) subjects reporting the use of anti-coagulant medicine. Figure 10 is a graphical representation of the use of other therapeutic medicine within VaD patients.

Figure 10: Use of Other Therapeutic Medicine within the VaD Sample Population



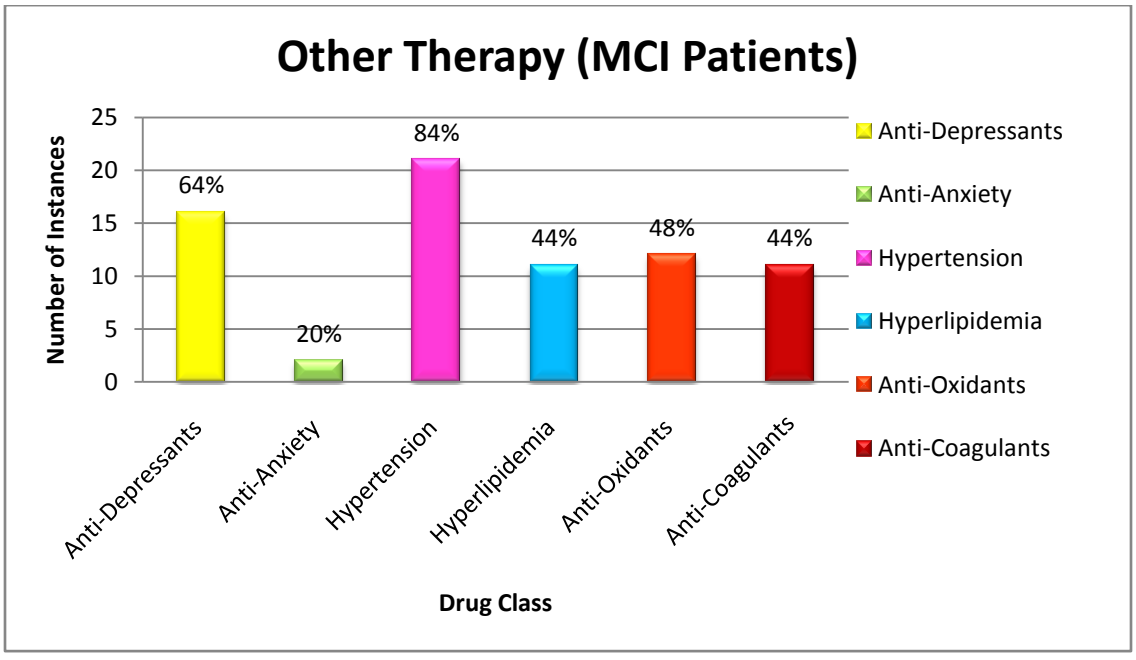
The retrospective chart review included the documentation of AD specific therapy on MCI patients. As a result, 1 subject uses Namenda®, 6 subjects use Aricept®, 2 subjects use Exelon® and 4 subjects use Razadyne ER®. No subjects were found to use both Namenda® or other forms of AChEIs. There were 13 subjects (44%) who did not use any AD specific medication. Figure 11 is a graphical demonstration of the fore mentioned results.

Figure 11: Use of Specific AD Therapy within the MCI Sample Population



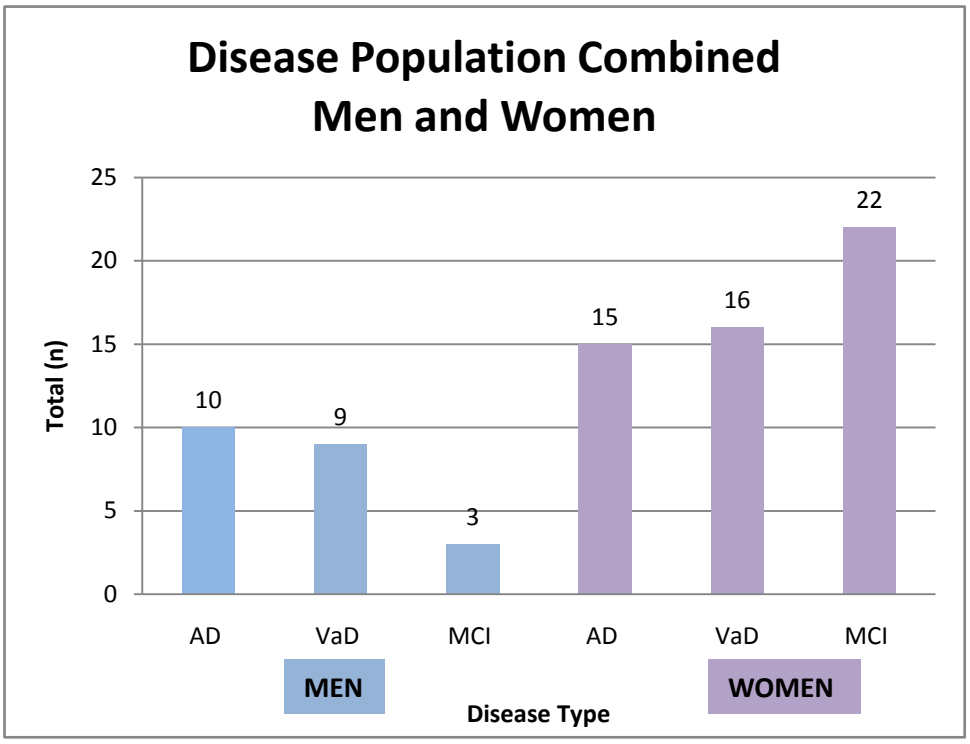
The retrospective chart review also included the documentation of other drug therapy commonly prescribed to MCI patients. As a result it was shown that 16 subjects (64%) use anti-depressants medication. The use of anti-anxiety medication was reported in 4 subjects (20%). Hypertension medication was used by 21 MCI subjects (84%). An additional 12 subjects (44%) reported the additional use of hypercholemia medication. The reported use of anti-oxidant medication in MCI patients was 12 subjects, representing 48%. There were 11 subjects (4%) reported the use anti-coagulants. Figure 12 is a graphical representation of the use of other therapeutic medicine within VaD patients.

Figure 12: Use of Other Therapy within the MCI Sample Population



Within each disease group, women were more prone as compared to men to suffer with dementia. Figure 13 is a side-by-side comparison.

Figure 13: Age Comparison within Each Disease State



Figures 14 and 15 compare the use of various medication of subjects diagnosed with dementia due to AD, VaD and MCI.

Figure 14: Comparison of AD Therapy Used within Each Disease State

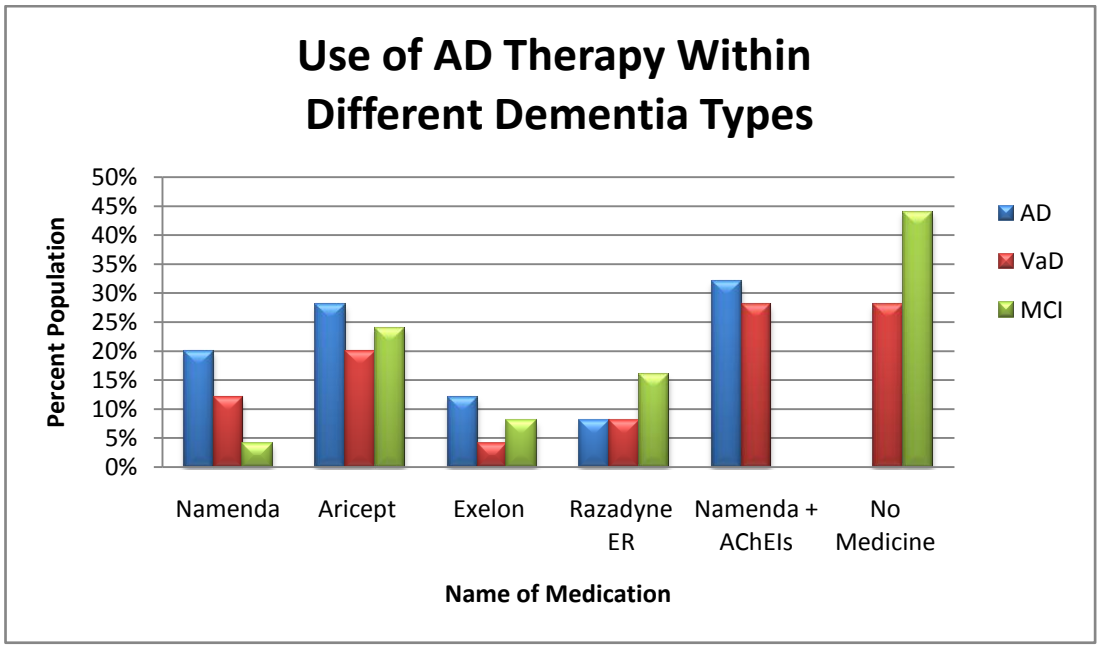
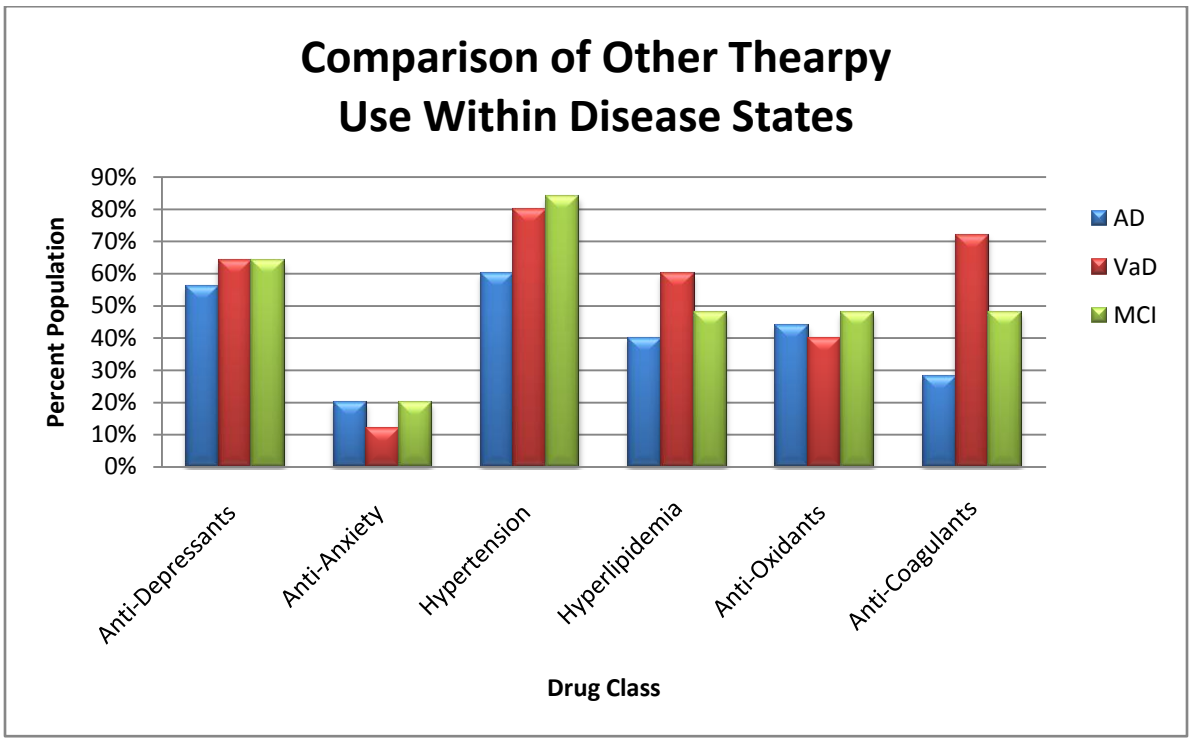


Figure 15: Comparison Other Therapy Used within Each Disease State



CHAPTER IV

DISCUSSION AND CONCLUSION

Dementia is a neurological disorder of the elder population that impairs cognitive function and subsequently leads to loss of self autonomy. Overall, the loss or decline in memory or cognitive function is caused by various mechanisms of neuronal cell death. Even though various types of dementia exist, distinction in symptom patterns and brain abnormalities are present. It is estimated that nearly half of all people in the United State 85 years of age and older will have some form of dementia (Herbert et al., 1995). AD is the most common dementia disorder among the elderly (Duron, 2008). Despite heroic efforts by scientist to search for answers, the rapid increase incidence of cognitive disorder remains to be so challenging that 148 billion dollars are dispersed annually to fund AD research (www.alz.org).

The treatments for patients with dementia varies according to the form of dementia diagnosed, i.e., AD, VaD, and MCI. This practicum report examined the differences in medicinal treatment in these three groups of patients in order to provide insight into current treatment options and determine current medicinal treatment trends. Figures 14 and 15 summarize and compares the use of various medications in subjects diagnosed with dementia. As these figures demonstrate, physicians prescribe medications based on the primary diagnosed cause of the dementia.

The reasons for the difference in prescribed treatment regimen are several. First, the prevalence of age-related dementia seems to differ by the amount one's education (www.alz.org). There is strong evidence that people with fewer years of education appear to be vulnerable to forming dementia. For example, one study has shown that there is a 15% increase of developing AD in people with less than 12 years education and 35% greater risk than people with 12 to 15 years education (Kukul et al., 2002).

Another possibility that could explain the difference in prescribed use of medications may be attributed to differences in socioeconomic factors and upbringing of the patients (www.alz.org). These factors include lack of income to buy medications or nutritious foods, sedentatry lifestyle, lack of cognitive stimulation, etc..

Patients who experience any form of dementia may also experience behavioral and personality changes, forgetfulness, confusion, inability to learn new material, paranoia, language difficulty and even motor activity problems (www.alz.org). Personality changes demonstrate the high use of anti-depressants in each category. Depression is usually a side effect with age-related dementia. When comparing the use of anti-depressant medication within the given types of dementia, use of antidepressants was quite common. It is often reported that frustration, struggles, and stress is frequent among the demented population. To slow the rate of memory loss, AChEIs seem to be an accepted use for the treatment of dementia. However, the fact remains that AChEIs have shown consistent and modest benefits for treatment of cognition impairment, but there is still no cure.

Hypertension and VaD have both positive and negative relationships. Research has shown than blood pressure rates were reported higher with developing dementia patients than non-demented patients (Skoog et al., 1996). Furthermore, research has also demonstrated a reduction in the incidence of dementia with antihypertensive treatments (Forette et al., 1998). The use of statin drugs to increase HDL shows promising benefits for dementia. According to a recent article high levels of good cholesterol in middle age people help maintain memory, thus, reducing the chances of developing age-related dementia (www.medheadlines.com). The goal of this practicum report is to address whether medicinal treatments vary significantly within each specific dementia type.

In summary, the average onset of any age-related dementia occurs primarily in persons 65 years and older but is more noticeable with age. The UNTHSC sample population is a direct reflection revealing the age range of Alzheimer's type dementia to be 61 to 93 years with an average of 79 years, Vascular Dementia type to be 68 to 94 year with an average of 80 years and Mild Cognitive Impairment ranging from 64 to 93 years with an average of 76 years. In this particular study, the sample population of each dementia types revealed women to have a higher incidence than men. Furthermore, within each dementia type, women were more susceptible particularly with MCI. The use of AChEIs is frequently used within each specified dementia. The use of Namenda® to is more visible in AD and MCI patients. Anti-oxidant medication is used minimally in all dementia types. Dementia side effects often entail depression, mood, and personality changes. The use of anti-depressant medication was frequently administered in each type of dementia. Contrary, the use of anti-anxiety medication was mild within the disease

states. Hypertension is also reported higher in patients developing dementia (Skoog, et al., 1996). Each dementia type showed use of anti-hypertensive drugs. Both MCI and VaD patients (80%) showed a more prevalent use of this medication over AD patients (60%). Because VaD patients have experienced some type of arterial occlusion, it is fair to assume that this group would use anti-coagulant and hypercholemia more so than other type of dementia. This trend was definitely seen within the AD, VaD and MCI sample population. VaD subject pool use of anti-coagulant medication towered over AD by 40% and MCI by 20%. This particular result is warranted given the risk factors before or after a vascular event. Further research is necessary to deem any foreseen trends significant.

CHAPTER IV

INTERNSHIP EXPERIENCE

My six-month clinical research internship was located at the University of North Texas Health Science Center in the Patient Care Center, specifically in the Department of Internal Medicine, Division of Geriatrics. The geriatric department provides specific care to patients over the age of 65 years and offers services, such as family conferences, to help cope with age-related diseases. Many clinical trials are conducted at this site which target typical age-related problems such as AD and rheumatoid arthritis. The trial of interest for me was specifically aimed at testing the safety and efficacy of the investigational drug, bapineuzumab, in elderly patients with mild to moderate AD. The geriatric division is led by devoted geriatrician, Dr. Janice Knebl DO, MBA. Her assistant, Barbara Harty, Geriatric Nurse Practitioner, serves as the passionate clinical research coordinator in several dementia related diseases. Ms. Harty is also a member of the UNTHSC Institutional Review Board, an assistant professor and my educator during my internship. The duration of my internship, two industry sponsored AD clinical trials and one investigator initiated study were ongoing.

Through this internship, I obtained vast knowledge and valuable experience on how human clinical trials are conducted and the roles of a principal investigator, research coordinator and the Institutional Review Board (IRB). The core of my internship was to serve as a clinical research coordinator (CRC). Therefore, I preformed the day-to-day tasks expected by a CRC, from recruitment, screening, preparation to the management of a clinical trial. The clinical trial that contributed to my experience was a Phase-3,

multicenter, randomized, double-blind, placebo-controlled, parallel group, efficacy and safety trial of Bapineuzumab. This trial was conducted in patients with mild to moderate Alzheimer disease who are carriers and non-carriers of Apolipoprotein E4. This clinical trial was complex and allowed me to truly learn the details involved in clinical research management. Duties expected were both direct and indirect with regards to study subjects. Direct duties included subject-coordinator rapport, such as recruitment, sample collection, adverse event reporting, informed consent process, vital signs assessment and monitoring during infusion visits and follow-up phone-calls. Other direct duties involved IRB, clinical monitor and study sponsor interactions. Indirect duties included protocol implementation, administrative duties, filing of case reports, management of study related files, inventory accountability, training and monetary/budget information. Some direct indirect duties are explained in detail below.

Training and Certification:

To participate in research with human subjects the UNTHSC IRB requires the comprehension and completion Collaborative IRB Training Initiative (CITI). Health Insurance Portability and Accountability Act (HIPAA) training is also required to have access to private patient information.

The UNTHSC Office of Clinical trials require Study Manager training for stipend compensation and doctor fee distribution, in which I obtained.

Upon sample collection, particularly blood samples, training was offered and completed for proper processing, shipping and packaging.

Occasionally, our study sponsor provided live training on documentation, protocol and procedure changes in which I attended via internet or phone. The study sponsor also provided Medidata training, a program specifically designed for data input of any trial related material.

Subject Recruitment and Screening

Potential subjects often came from UNTHSC geriatric clinic doctor referrals, active patients of the Texas Alzheimer's Research Consortium (TARC) or by study recruitment ads. I quickly learned how to screen potential subject's medication chart for trial eligibility. If a subject met clearance through inclusion/exclusion criteria, Ms. Harty demonstrated how to explain the concept of a clinical trial without placing pressure to join the study. She stressed that the drug was investigational and that participation was strictly voluntary. If necessary, Ms. Harty offered advice and detailed explanation of AD progression. If a subject was unable to join our study, their names were kept for further studies if permission was granted.

Implementation of Study Protocol Procedures:

During my internship, I was fortunate to observe Ms. Harty efficiently explain the details of the informed consent. She verbally gave the subject adequate information concerning the study, allowed for the subjects to consider all options and answered any questions the subject may have. Ms. Harty double-checked for patient and caregiver comprehension and then obtained signatures and proof of participation and voluntary action. A copy of the informed consent was given to each subject.

At each visit, I assisted Ms. Harty in collecting, processing and packaging blood samples for laboratory analysis. Guidelines were followed according to study sponsor and the secondary laboratory packaging of biological samples regulations.

During certain study visits, an electrocardiogram (EKG) was obtained. I reviewed and received training to successfully perform an EKG and to transmit the results.

At the end of each study, I ensured that the subject and caregiver would receive their stipend supplementation. Ms. Manider Malik, Ms. Harty's assistant, provided adequate training on the use of Study Manager for subject stipend request. Study Manager is a program used by UNTHSC Office of Clinical Trials that tracks monetary activities such as subject and doctor compensation.

Management Duties:

Subject binder preparation was an important component of assuring that the visit was properly conducted. I was taught to place all necessary documents, workbooks and study visit kits together before each patient arrived. I would hand all materials to the corresponding doctors as per protocol procedure. By doing so, I inadvertently learned to keep track of inventory, such as laboratory kits, airway bills, shipping cartons, test booklets, source documents, subject binders, EKG cards and any other study related material.

Our study sponsor frequently asked for weekly updates regarding the study. As a result, a weekly fax was sent to them that included significant information of our enrollment status.

Ms. Harty also kept me well informed of changes out study sponsor may have required. Some emails required necessary action in which I completed quickly. All items ensured successful completion of our study.

Occasionally, our study subject would inform us of unexpected events. For example, if a subject took a bad fall, I learned how to properly notify our study sponsor by filling out a On-site Serious Adverse Event (SAE). A copy of the SAE was sent to our IRB as well. If a subject missed a study visit due to bad weather and the subject fell out of the study window, a protocol deviation had to be filed. Protocol deviations had to be sent to both

out study sponsor and IRB and approval must be attained before commencing with the study. During my internship, many unforeseen circumstances occurred allowing for practice of filing such documents.

Regulatory Duties:

IRB Interaction:

During my internship, I had the opportunity to participate in many different IRB regulatory administrative duties. Upon my arrival, the study was scheduled up for a continuing review. If a study is approved with continuing review, it means that the study contains a moderate risk level and the IRB wishes to review the study, in this case, every six months. I was fortunate to attend an IRB meeting in which I witnessed a continuing review process.

SAEs that occurred outside of our specific site were also reported to us and subsequently our IRB. I learned firsthand how to complete and submit off-site SAEs to our IRB. I developed a tracking system for ease of reporting such documents.

For my personal practicum report, I participated directly in my own submission of an expedited review. In addition, I actively participated the implementation of protocol design, source documents, informed consent and IRB application for the second investigator initiated study, For HERs Project.

Protocol and Procedural Modifications:

Because a clinical trial is investigating a new drug, it is common for the study sponsor to make modifications to the protocol, procedure and even the informed consent. For example, if an unexpected serious adverse even occurred; we were to make changes to our existing informed consent document. In order to do so, we must adhere to the IRB rules and regulations. Once the IRB approved our changes, we were to notify each subject and reconsent them. During my internship, I had the opportunity experience changes in protocol design, informed consent and other documents. This provided powerful insight of how a study sponsor might intervene if the investigational drug becomes too perilous.

Study Sponsor and Clinical Monitor Communication:

I observed and even participated in several outreaches to both our study sponsor and clinical monitor regarding issues that arose with our clinic site. Such problems included protocol deviations and SAE reporting. In my observation, both the study sponsor and clinical monitor were quick in responding to our queries.

During the course of my internship, I was able to participate in a clinical monitor visit. I was able to witness the expectation, hard work and effort necessary to become a clinical monitor. My management training I received during my internship allowed for a very smooth visit with our monitor.

Meetings:

My internship allowed me to attend departmental, institutional, study sponsor and coordinator meetings. During these meeting I learned of the problems that were faced with other studies and how to properly address such issues.

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IV. APPENDIX

INTERNSHIP DAILY ACTIVITY LOG

December 3, 2008- Wednesday

Meeting with Dr. Janice Knebl, Ms.Barb Harty and Dr. Patricia Gwirtz about the internship and what to expect.

Barb Harty briefed me on my study duties.

Discussed possible projects for my thesis.

December 5, 2008- Friday

Introduction Day.

Brief overview of the Study.

Barb introduced me to key personnel and showed me where I would be working from.

Started to read the regulatory binder.

December 8, 2008- Monday

Maninder Malik explained what is to be done before patient visits.

She showed me where to get my source documents and how a patient data profile is maintained.

I read through the source documents and workbooks to get a understanding before a major visit tomorrow.

Learned about the different study arms of the clinical trial.

December 09, 2008- Tuesday

Patient came in for the clinical trial visit.

Shadowed Dr. Hall, Lisa Alvarez, and Barb Harty as the interviewed according to the workbooks.

Shadowed Dr. Knebl as she preformed the physical examination of the patient.

December 10, 2008- Wednesday

Training on Mediata Data Entry System.

Maninder showed me how to input the workbook data into the Medidata System.

She also showed me how to interpret the source documents.

December 11, 2008- Thursday

Read the Regulatory Binder.

Read the Covance Lab procedure protocol.

Took a dvd home for training on EKG testing and reporting techniques.

Printed out the Source Documents for visit.

December 12, 2008- Friday

Shadowed while Barb as she went over the informed consent form with the patient and caregiver.

Barb accessed the patient's vitals, medical history and inclusion/exclusion criteria.

Dr. Knebl preformed a physical ability test.

Source Documents and workbooks completed by appropriate personnel.

Labs were collected and Maninder showed me how to prepare medical samples according to protocol and proper shipping.

December 15, 2008- Monday

Read the Regulatory Binder.

Maninder and I both entered data from source documents and workbooks into Medidata.

She briefly went over patient compensation for visit.

December 16, 2009- Tuesday

Barb explained in detail how this clinical trial works. She gave me important information to remember.

She explained what and how to report serious adverse events and specific timelines to which we need to file necessary documents.

Maninder showed me how to fill out the report for UNTHSC IRB submission.

December 17, 2008- Wednesday:

Continuation Regulatory Binder reading.

Continuation Correspondence Binder reading.

December 18, 2008- Thursday

Barb was out of the office.

Personal research on clinical trials.

December 19, 2008- Friday

Preparation for Monday's infusion visit.

Source documents and workbooks were updated into the patients data profile.

Maninder showed me where lab kits were kept.

Barb gave me reading material to about the trial to read over the Christmas Holiday.

December 22, 2008 – January 03, 2005

I left out of town for the Christmas Holiday, with Barb's consent.

I did personal reading on the conductance of human clinical research.

Browsed the internet for proposal and theiss guidelines/requirements.

January 05, 2009- Monday

Because of the holiday break we were bombarded with safety reports.

Maninder once again showed me how to complete them.

Before submission to UNTHSC IRB the safety reports were checked by Maninder for accuracy.

January 06, 2009- Tuesday

Maninder showed me how to keep track of workbooks, kits, etc..

Had some training on Medidata.

Read on how to properly process medical samples for next weeks visit.

January 07, 2009- Wednesday

Read the correspondence binder.

Watch a tutorial video on how to collect an EKG.

Learned about processing of biological samples.

January 08, 2009- Thursday

Learned about Serious Adverse Events both on-site and off-site.

Maninder showed me how to complete safety reports received from other study sites.

I was showed where to get the forms for SAEs.

My work was double-checked by Barbara.

January 09, 2009- Friday

Continuation of SAE reporting.

Read a journal article about trends in clinical research.

Began to familiarize myself with the correspondence notebook.

January 12, 2009- Monday

Preparation of study binder for tomorrow's study visit.

Made sure all documents were put together in order of events.

Double checked for kits, airway bills and packaging cartons.

January 13, 2009- Tuesday

Study visit day.

Shadowed Barb, Dr. Knebl, Dr. Hall and Lisa as they completed necessary source documents for clinical trial.

Stayed with patient throughout the duration of study treatment to make sure no adverse events would occur.

January 14, 2009- Wednesday

More Medidata training.

Enter data of source documents into Medidata system.

Read about our clinical trials history.

January 15, 2009- Thursday

Continued to familiarize myself the study reference binder.

Started going through patients profiles.

Made sure all Medidata information was entered.

January 16, 2009- Friday

Study manager training.

Read Maninder's Proposal.

Requested Dry Ice for Tuesday's visit.

Went over Inclusion/Exclusion criteria for subject recruitment

January 19, 2009- Monday

Received training on EKG testing and submission

Prepared for tomorrow's visit by putting together all workbooks, kits and source documents.

January 20, 2009- Tuesday

Study Visit.

Shadowed Barb as she went over the Informed Consent with both the subject and caregiver

Maninder showed me how to process, package and ship biological samples

Learned where to call for sample pick-up

January 21, 2009- Wednesday

Entered Data into Medidata

Entered Stipend information into Study Manager

January 22, 2009- Thursday

Barb was out of office.

Continued to read study visit material.

January 23, 2009- Friday

Ordered supplies.

Continued reading.

January 26, 2009- Monday

Preparation of study binder for tomorrow's study visit.

Made sure all documents were put together in order of events.

Double checked for kits, airway bills and packaging cartons.

January 27, 2009- Tuesday

Study visit day.

Shadowed Barb, Dr. Knebl, Dr. Hall and Lisa as they completed necessary source documents for clinical trial.

Stayed with patient throughout the duration of study treatment to make sure no adverse events would occur.

January 28, 2009- Wednesday

Screening visit- talking to subjects about volunteering to be in our research study

Enter data of source documents into Medidata system.

January 29, 2009- Thursday

Subject Recruitment: Looked over doctor referred patients files to see if they are eligible for our study.

Created a list for Barb to talk to potential subjects regarding the study.

January 30, 2009- Friday

SAE report completion, filing and updating.

February 2, 2009- Monday

Preparation Day.

Gathered all necessary workbooks and source documents for tomorrow's visit.

Attended an IRB meeting in which I observed the continuing review process.

February 3, 2009- Tuesday

Shadowed Dr. Knebl and Barb while they followed the protocol for today's visit.

Stayed with the patient throughout the duration of the study drug treatment.

Monitor the patient for any adverse events to report.

Sent data sample off for testing.

February 4, 2009- Wednesday

SAE reporting.

Read various journals and browsed internet to search a topic for my internship practicum report.

Continued to familiarize myself with the correspondence binder.

February 5, 2009-Thursday

Entered data in MEDIDATA

Entered stipend information into Study Manager

February 6, 2009- Friday

Started working on CITI training.

February 9, 2009- Monday

Preparation for Tomorrow's visit.

Place all workbooks, source documents and gifts for patient in study binder.

Made sure all kits, airways bills and packaging documents were in order.

Met with Dr. Knebl about potential thesis projects.

February 10, 2009- Tuesday

Infusion visit stayed with patient all day through the duration of the visit.

Checked medical books for discrepancies.

Packaged blood samples for clinical testing.

CITI Training completed.

February 11, 2009- Wednesday

Manider taught me about study manger, a program used to ensure that both the subject and caregiver received their visit compensation.

Enter workbook and source document data in to medidata system.

Completed IRB Exempt paper work.

February 12, 2009- Thursday

Personal research for thesis proposal.

Did plenty of reading about current treatment options for people with AD.

February 13, 2009 Friday

Personal research for thesis proposal.

Did plenty of reading about current treatment options for people with AD.

February 16, 2009- Monday

Replenishment of kits, workbooks, and packaging supplies.

Attended EMR training.

February 17, 2009- Tuesday

Completion of Safety Reports.

Attended a mandatory Medidata meeting.

Met with Jim Moss about study manager issues.

February 18, 2009- Wednesday

Attended a teleconference.

Made copies of informed consent.

SAE report.

February 19, 2009- Thursday

Personal Day.

Research for my thesis.

February 20, 2009- Friday

Filing and completion of SAE Reports.

Interaction with IRB about specific questions.

February 23, 2009- Monday

Teleconference with our sponsor.

Preparation of new subject study binder.

February 24, 2009- Tuesday

Screening visit of potential new subject.

Shadowed Barb while she explained the informed consent.

February 25, 2009- Wednesday

EMR screening for potential subjects.

February 26, 2009- Thursday

Answered and queries in Medidata

Reviewed subject binders for missing data.

February 27, 2009- Friday

Looked up articles for my thesis

March 02, 2009- Monday

Took inventory of supplies.

SAE reporting

Ordered supplies

March 03, 2009- Tuesday

Attended the IRB meeting.

March 04, 2009- Wednesday

Preparation for new subjects screening.

Place all workbooks, source documents and in study binder.

March 05, 2009- Thursday

Completion of Safety Reports.

Exempt Approval from IRB regarding my thesis project was approved.

March 06, 2009- Friday

SAE reporting and filing.

Took time off to complete my proposal now that my project was approved by the IRB.

March 09, 2009- Monday

Assisting in the creation of an investigator initiated study.

Filled out IRB new research study paper work.

Created Source Documents

March 10, 2009- Tuesday

Protocol Exemption filing. Subject fell out of window.

March 11, 2009- Wednesday

Assisted in editing of the Informed Consent of the new research study.

SAE Reporting.

March 12, 2009- Thursday

Preparation for Clinical Monitor Visit.

Double checking subject study binders for signatures, missing information, etc.

SAE reports.

March 13, 2009- Friday

Preparation for Clinical Monitor Visit.

Double checking subject study binders for signatures, missing information, etc.

Started Reviewing

March 16, 2009- Monday

Preparation for clinical monitor visit.

Review of subject binders- 302 Arm

March 17, 2009- Tuesday

Preparation for clinical monitor visit.

Review of subject binders- 301 Arm

March 18, 2009- Wednesday

Clinical Monitor Visit.

SAE Reporting

March 19, 2009- Thursday

Clinical Monitor Visit.

March 20, 2009- Friday

Clinical Monitor Visit.

March 23, 2009- Monday

Patient Visit.

Made sure all procedures and examinations were performed.

March 24, 2009- Tuesday

Patient Visit

Monitored Doctors as they performed testing.

March 25, 2009- Wednesday

Outstanding document filing.

Sent our site updated copies of licenses.

SAE reporting.

March 26, 2009- Thursday

Screening Visit

Witnessed the informed consent process.

March 27, 2009- Friday

Helped enter data into Medidata.

March 30, 2009- Monday

Patient Visit

March 31, 2009- Tuesday

Patient Visit

Filing of Medical Exemption form.

April 1, 2009- Wednesday

Screened patients for possible entrance into study

April 2, 2009- Thursday

Patient Chart Review for thesis project

April 3, 2009- Friday

Patient Chart Review for thesis project

April 6, 2009- Monday

Patient Chart Review for thesis project

Preparation for study visit tomorrow.

April 7, 2009-Tuesday

Patient Visit

Shadowed each doctor as they preformed study procedures.

Monitored patient during infusion.

April 8, 2009- Wednesday

Patient Chart Review for thesis project.

April 9, 2009- Thursday

Entered study booklets into medidata.

Review of study manager to ensure patients stipends were processed.

April 10, 2009- Friday

Personal Research for thesis.

April 13, 2009- Monday

Teleconference training.

April 14, 2009- Tuesday

Patient Chart review for thesis.

April 15, 2009- Wednesday

Patient Chart review for thesis.

April 16, 2009- Thursday

Preparation for patient visit.

Gathered all booklets and study kits.

April 17, 2009- Friday

Research for my thesis

April 20, 2009- Monday

Patient Visit.

Shadowed doctors perform all study procedures.

Assisted in the collection of biological samples.

April 21, 2009- Tuesday

Patient Visit.

Shadowed doctors as they preformed all study procedures.

April 22, 2009- Wednesday

Teleconference training.

Paper filing.

April 23, 2009- Thursday

Routine Screening of Patients thru EMR

Patient Chart Review for thesis topic

April 24, 2009- Friday

Answered any queries in Medidata

April 27, 2009- Monday

Preparation for study visit.

Place all workbooks, source documents and gifts for patient in study binder.

Made sure all kits, airways bills and packaging documents were in order.

SAE reporting.

April 28, 2009- Tuesday

Study visit.

Shadowed study staff to ensure that all study procedures were followed.

Monitored patient during infusion.

April 29, 2009- Wednesday

Personal research for my thesis.

Patient screening for recruitment.

Enter data into medidata

April 30, 2009- Thursday

Personal Day to finish my thesis

May 01, 2009- Friday

Personal Day to finish my thesis

May 04, 2009- Monday

Preparation for two subject visits.

Placed all material in study binders and organized a schedule since multiple procedures had to be done.

May 05, 2009- Tuesday

Double Patient Visit.

Shadowed doctors to ensure all study material, booklets and procedures were completed.

Assisted in collecting and sampling of biological material.

Stayed with both subjects during infusions.