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The Effect of Anticholinergic Burden on Functional Outcomes in Patients with Moderate to Severe Alzheimer's Disease

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Abstract

THE EFFECT OF ANTICHOLINERGIC BURDEN ON FUNCTIONAL OUTCOMES IN PATIENTS WITH MODERATE TO SEVERE ALZHEIMER'S DISEASE

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

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Background: Alzheimer's disease (AD) is the most common form of dementia and is characterized by a progressive loss of memory, judgment, and thinking in older adults. The current treatment is cholinesterase inhibitors, which increase acetylcholine at the synapse. Medications with anticholinergic (AC) activity are given for a variety reasons including for the treatment of comorbid conditions or side effects of cholinesterase inhibitors (ChEIs).

These drugs inhibit acetylcholine in the brain. Studies have shown the detrimental outcomes of using AC medications with ChEIs in older adults. Moreover, older patients take more medications and have an increased risk of developing AC toxicity as these effects are additive. The association between AC burden with functional, cognitive, and behavioral outcomes bears further evaluation.

Methods: This study is a retrospective observational study that investigated the effect of AC medications on function, cognition, and behavior. Data was collected from charts on dementia patients who resided at Piedmont Geriatric Hospital. Descriptive statistics and GEE regression were performed using MS Excel 2007 and SPSS 18.0.

Results: There were a total of 83 subjects included in this study with a median age of 77 years old and with a median length of stay of 536 days. 33.7% of the patients were taking cognitive-enhancing medications. The analysis found that AC burden was not a significant predictor of functional, cognitive or behavioral decline.

Conclusion: The minimal amount of literature on this association, suggests that AC burden may have negative consequences on function, cognition and behavior in dementia patients. The study results provided inconclusive evidence about the association of AC burden on poorer functional, cognitive and behavioral outcomes. Future research in this field is needed to determine if there is a true association between worsening outcomes and AC burden.

Chapter 1

Introduction

1.0 Chapter Introduction

This diversified chapter introduces Alzheimer's disease, anticholinergic drugs and burden as well as the barriers to research. Dementia, especially Alzheimer's disease (AD), is a chronic disease that lacks a cure. Cholinesterase inhibitors (ChEIs) are a symptomatic treatment for AD. Other drugs with anticholinergic properties are typically used as treatment for comorbid conditions associated with AD. This second class of drugs, anticholinergic (AC) medications, has been associated with negative outcomes in older adults. There is some evidence and suggestion that these AC medications may be associated with negative outcomes in dementia patients as well, but the link between dementia and negative effects as a result of anticholinergic properties is not well defined due in part to barriers to conducting research in patients with dementia. One potential reason for this lack of evidence is difficulty in recruiting older dementia patients to participate in studies.

1.1 Alzheimer's disease

Alzheimer's disease (AD) is the leading cause of dementia in older adults, accounting for 60 to 80% of all dementia cases.

The Alzheimer's Association estimates that currently over 5.3 million Americans suffer from AD and that by 2050 an estimated 11 to 16 million people over the age of 65 will be affected (Alzheimer's Association, 2010).

AD is a progressive neurodegenerative disorder that has particular clinical and pathological changes associated with it. The disease damages the limbic structures, specifically the hippocampus, cholinergic system and neocortical pathways (Maccioni et al, 2009). Clinically this is characterized by a progressive loss of memory, judgment, and thinking in the older population. This disease affects each individual differently. The most common pattern of progression starts with difficulty remembering new information possibly followed by memory loss, loss of executive functioning, difficulty in completing familiar tasks, confusion with spatial information, problems with language and perception, withdrawal from social activities, and changes in personality (Alzheimer's Association, 2010). It is suggested that the symptomatic course is generally 5 to 10 or more years from the time that the memory deficits appear. Other evidence suggests that a seven year pre-clinical decline occurs (Shah et al, 2008).

The mechanism of neurodegeneration is not well understood, but it is suggested that the neurodegenerative process starts with damage to the synaptic terminals that leads to eventual neuronal loss (Maccioni et al, 2009). Loss of the synapse occurs and is correlated with cognitive decline. This damage is caused by the formation and proliferation of plaques consisting of amyloid β (Aβ) peptides and neurofibrillary tangles composed of tau proteins (Maccioni et al, 2009).

The disease does not have a definitive cause and several theories have been developed to attempt to understand and explain the basis of Alzheimer's disease. The most widely held theory is the

Amyloid hypothesis in which AD is caused by the formation of plaques made by the deposition of beta-amyloid peptides (Aβ) in brain tissue. These plaques are misfolded from the natural occurring amyloid peptides. In addition, it is suggested that the formation of neurofibrillary tangles by tau proteins is a result of the imbalance of Aβ production and clearance (Hardy et al, 2002). The amyloid hypothesis is compelling because the gene for the amyloid beta precursor APP is located on chromosome 21. The regions linked to one type of familial AD are also on chromosome 21. Furthermore, Down syndrome patients who have an extra copy of this chromosome present with disorders similar to AD by the age of 40. Moreover, research has found that there are genetic defects in the genes that code for APP in some types of familial AD. In addition, genetic defects are also found in certain proteins, *presenilin 1* and *2* which produce the enzyme that produces one form of Aβ. It has been shown that mutations in *presenilin 1* & *2* increase the levels of Aβ (Ropper et al, 2005).

One of the oldest hypotheses is the cholinergic hypothesis in which AD symptoms are caused by a deficiency in the production of acetylcholine. This was based on the work of Whitehouse et al in 1982, who found a selective loss of basal forebrain neurons in AD patients (Shah et al, 2008). These neurons are the major source of cholinergic innervations in the cerebral cortex. Cholinergic innervations of the brain extend to the cortical and hippocampal regions. These regions are important to the processes of memory, language, and visuospatial skills. Cholinergic neurons develop from the nucleus basalis of Meynert to both the hippocampus and the cortex. Transmissions through these innervations are very important in normal cognitive functioning (Kay et al, 2005A). The degeneration of the cholinergic circuits and impaired cholinergic transmission has been associated with cognitive dysfunction. Therefore, the first-generation anti-Alzheimer's medications are based on this hypothesis and work to preserve acetylcholine

activity. This class of drugs reversibly inhibits the enzyme acetylcholinesterase, which is responsible for the breakdown of acetylcholine at the synapse into choline and acetate. The inhibition of this enzyme prolongs the activity of the existing acetylcholine at the synapse thereby perpetuating the signal longer. There is some evidence that these drugs may stabilize the disease for a short period of time, but there is no evidence of disease modification (Shah et al, 2008). The proposed mechanism of stabilization is based on the β-amyloid-cholinesterase-cyclo-oxygenase-2 cycle. The idea is that β-amyloid increases the expression of both AChE and cyclo-oxygenase 2 (COX-2) in the brain. The inhibition of AChE by ChEIs increases the release of APP and reduces β-amyloid deposits as well as COX-2 expression, which is suggested to cause inflammation in AD (Giacobini, 2001). This class of medications, acetylcholinesterase inhibitors (AChEI), contains four drugs that are still on the market. The first is tacrine that is rarely used as it requires dosing four times per day and has been linked to hepatotoxicity. The other three drugs include donepezil, galantamine and rivastigmine. These drugs have greater efficacy compared to tacrine. The most commonly prescribed AChEI is donepezil, which has indications for mild through severe disease. The other AChEIs have an FDA approved indication only for mild and moderate disease.

There is a second class of drugs that is used for the treatment of AD. This class, N-methyl-D-aspartate (NMDA) receptor antagonists are used based on the premise that the release of glutamate in the CNS may play a role in excitotoxic reactions thereby leading to cell death (Koda-Kimble et al, 2005). Memantine, an uncompetitive antagonist that works by blocking glutamatergic neurotransmission by antagonizing this receptor, is the only medication of this class currently on the market in the US. It has an indication for monotherapy in moderate to

severe disease and studies suggest when combined with AChEIs there is more improvement in cognition and ADLs than with memantine alone.

A review of the clinical trial data by a Cochrane review in 2006, found that after treatment for 6 months with the three AChEIs, there were some improvements in cognitive functioning, behavior and function. The positive improvements were mild or small with a 2-3 point decrease on the ADAS-Cog (Birks, 2006), the gold-standard in measurement of cognitive functioning in AD trials. These mild improvements on assessments do not translate to significant clinical improvements. Furthermore, adverse events were not uncommon. There was a significant difference in the percentage of treatment patients, 29%, who withdrew due to adverse events compared to the placebo group, 18%. There were forty-seven types of adverse events that occurred among the several AChEI trials. The most commonly reported events include abdominal pain, anorexia, abnormal dreams, asthenia, diarrhea, dizziness, fatigue, headache, insomnia, muscle cramp, nausea, syncope, tremor, peripheral edema, vertigo, weight loss and vomiting. These adverse events occurred significantly more in treatment patients than in placebo (Birks, 2006). Moreover, in a study by Gill et al it was found that as many as 51% to 78% of the older adults assessed would not have been eligible to participate in the ChEI clinical trials. Additionally, they found that their cohort was older and more likely to be living in long-term care compared to the clinical trial participants (Gill et al, 2004). Finally, cost-effectiveness studies that have been completed have shown that these medications may not be cost-effective. Also, the cost-savings associated with reducing the time spent in full-time care does not balance the cost of the treatment (Loveman et al, 2006).

1.2 Anticholinergic Medications:

1.2.1 Definition and Exposure

Anticholinergic (AC) medications play an important role in patients with Alzheimer's disease as they are frequently added to medication regimens to treat comorbid conditions. These drugs, as the name would suggest, antagonize cholinergic receptors. There are two types of cholinergic receptors, muscarinic and nicotinic. There are five subtypes of muscarinic receptors M1-M5; three of which are important in cognitive functioning (Katzum BG, 2001). These include M1, M2 and M4, which are located CNS. All of the muscarinic receptor subtypes are distributed throughout the brain. The M1 subtype is most abundant in the CNS, especially the hippocampus, neocortex, and the neostriatum. The M2 receptor is located throughout the brain and the M4 specifically in the neostriatum. The M5 are localized to the hippocampus with projections in the substantia nigra, pars compacta and ventral tegmental nuclei. The M3 subtype is the only one that has low levels in the brain. Pharmacological studies that investigated the role of these receptors found that in M1 knockout mice there are impairments in spatial memory and severe deficits in working memory. In M2 knockout mice, impaired behavioral tasks requiring working memory and impaired regulation in cholinergic functioning was seen. Furthermore, studies have shown that blockade of M1 and M2 receptors is associated with increased amyloid plaques and neurofibrillary tangles compared to normal controls (Kay et al, 2005A; Perry et al, 2003). Other studies have linked M4 receptors to regulation of acetylcholine levels. Moreover, these three subtypes may be involved in mediating cholinergic effects on motor and sensory processes (Kay et al, 2005A). Additionally, one study suggested that antimuscarinic activity may increase amyloid plaques. This is based on evidence that activation of M2 receptors

increases the amyloidogenic activity of two important secretases that are known to cleave APP into a more aggregative form of amyloid. A study in Parkinson's disease patients found that chronic use of antimuscarinics was associated with higher rates of plaque and tangle formation (Perry et al, 2003).

The aging process leads to a cholinergic deficit that may explain some of the increased sensitivity to medications that block muscarinic receptors. There is some evidence that there are age-related declines in M1 receptors. One study found that the density of the M1 receptor subtype was 50% lower in an 82 year-old compared to a 19 year-old (Kay et al, 2005A). In addition, age-related physiologic changes affecting drug absorption, distribution, metabolism and elimination processes may alter responses to drugs compared to younger counterparts. Specifically, muscle metabolism is decreased and leads to increased fat deposition (Han et al, 2008), which affects the distribution of drugs in the body. In terms of drug metabolism, one study suggests that in older adults over 70, there may be as much as a 30% decrease in metabolism (Sotaniemi et al, 1997). Elimination processes are altered with age, chronic disease and certain medications. Hepatic clearance is more likely to be prolonged with age, specifically in drugs that undergo phase 1 metabolism. Those that undergo phase 2 only, are not typically affected. In renal elimination, it is estimated that creatinine clearance decreases at an average 8 ml/min/decade after the age of 30 (Ruscin, 2009). This change decreases renal elimination of some medications. Therefore there is an increased exposure to a drug and its metabolites in an older adult. Furthermore, there is decreased functioning of cholinergic brain receptors and increased permeability to the blood brain barrier (BBB) (Han et al, 2008). In younger counterparts, the BBB is made up of endothelial cells with tight junctions, which only allow small, unpolarized, lipid-soluble molecules to pass through. As a person ages, these cells begin

to shrink and the tight junctions allow for the creation of channels which allow larger, more polarized molecules into the brain. Other factors such as stress, comorbid diseases and some medications may increase the permeability of the BBB.

There are several medications with AC properties and this is shown in Table 1, which is compiled from the literature (Zarowitz et al, 2007; Ness et al, 2006; Lechevallier-Michael N et al, 2004).

Table 1: Sample list of medications with AC properties

Generic Name	Brand Name	Generic Name	Brand Name
Antihistamines		**Benzodiazepines**	
Chlorpheniramine	Chlor-Trimeton	Alprazolam	Xanax
Dexchlorpheniramine	Polaramine	Chlordiazepoxide	Librium
Diphenhydramine	Benadryl	Diazepam	Valium
Hydroxyzine	Vistaril/Atarax	Flurazepam	Dalmane
Promethazine	Phenergan	Oxazepam	Serax
Fexofenadine	Allegra	**Corticosteroids**	
Meclizine	Antivert	Dexamethasone	Decadron
Loratadine	Claritin	Hydrocortisone	Cortef
Doxylamine	Unisom	Prednisolone	Orapred
Antimuscarinics		**Gastrointestinal**	
Oxybutynin	Ditropan	Atropine	
Tolterodine	Detrol	Belladonna Alkaloids	Donnatal
Darifenacin	Enablex	Cimetidine	Tagamet
Solifenacin	Vesicare	Clindinium-chlordiazepoxide	Librax
Trospium	Sanctura	Dicyclomine	Bentyl
Cardiovascular		Hyoscyamine	Levsin/Levsinex
Captopril	Capoten	Metoclopramide	Reglan
Digoxin	Lanoxin	Rantidine	Zantac
Diltiazem	Cardizem	**Immunosuppression**	
Dipyridamole	Norpace	Azathioprine	Imuran

Generic Name	Brand Name	Generic Name	Brand Name
Furosemide	Lasix	Cyclosporin	Neoral/Sandimmune
Hydrochlorothiazide	Microzide	**Antibiotic**	
Isosorbide mononitrate	Imdur	Ampicillin	
Nifedipine	Adalat/Procardia	Cefoxitin	Mefoxin
Triamterene	Dyrenium	Clindamycin	Cleocin
Warfarin	Coumadin	Cycloserine	Seromycin
Anticonvulsants		Gatifloxacin	Tequin
Phenobarbital		Gentamicin	Garamycin
Antidepressants		Moxifloxacin	Avelox
Amitriptyline	Elavil	Piperacillin/Tazobactam	Zosyn
Desipramine	Norpramin	Tobramycin	Nebcin
Doxepin	Sinequan	Vancomycin	Vancocin
Imipramine	Tofranil	**Muscle Relaxants**	
Mirtazipine	Remeron	Carisoprodol	Soma
Nortriptyline	Aventyl/Pamelor	Chlorzoxazone	Paraflex
Trazodone	Desyrel	Cyclobenzaprine	Flexeril
Paroxetine	Paxil	Metaxalone	Skelaxin
Phenelzine	Nardil	Methocarbamol	Robaxin
Antipsychotics		**Parkinson's Disease**	
Clozapine	Clozaril	Amantadine	Symmetrel
Olanzapine	Zyprexa	Benztropine	Cogentin
Thioridazine	Mellaril	Trihexyphenidyl	Artane
Narcotic Analgesics		Methyldopa	Aldomet
Codeine		**Respiratory**	
Oxycodone	OxyContin, Percodan	Theophylline	Theo-24/Uniphyl/Theolair
Hydrocodone	Vicodin		

As shown there are several medications, including warfarin and antibiotics, that one would not typically consider as having AC properties. While relatively comprehensive, this list is only a sample as many medications are not included including newer ones such as fesoterodine.

1.2.1.2 Anticholinergic Burden

The term anticholinergic burden (AC burden) refers to the cumulative effect of taking multiple medications that block muscarinic receptors in the cholinergic nervous system. As discussed in the previous section, AC medications are believed to be hazardous to older adults, especially those with dementia. There is an additional issue of the cumulative effects of these medications. The concern of AC toxicity resulting from cumulative AC burden of multiple medications is a real issue for older adults (Kay et al, 2005A). The evidence in the literature provides some insight as to the seriousness of AC burden. Han et al found that AC burden was significantly associated with poor performance on memory and executive tasks, specifically the Hopkins Verbal Recall Test (HVRT) and the Instrumental Activities of Daily Living (IADL) (Han et al, 2008). A study by Ancelin et al showed that continuous use of AC medications for greater than one year was independently associated with poorer performance on attention, short-term memory and visuospatial construction (Ancelin et al, 2006). Burden is not an issue relating to only long-term use of medications with AC properties. Short-term studies show that the cumulative burden effects in older adults taking AC drugs for at least two weeks was associated with declines in visual memory, verbal fluency, global cognitive function, and on activities of daily living scales (Han et al, 2008). Recent studies have found that the cumulative effect of AC medications is strongly associated with falls in hospitalized older adults (Nebes et al, 2007). The literature suggests that older adults in the community are also at risk as many medications that are most commonly prescribed have antimuscarinic properties (Lechevallier-Michael et al, 2004). Also, many older adults use over the counter drugs with AC effects (Nebes et al, 2007).

1.2.1.3 Factors Influencing AC Burden

There are many factors that can influence AC burden including pharmacokinetic and pharmacodynamic changes, polypharmacy with medications that have AC properties, drug interactions, comorbid disease states, especially dementia, specific drug exposure and the integrity of the blood brain barrier. Polypharmacy or the use of multiple medications is a common problem in the older adult population. As mentioned earlier, older adults have an increased sensitivity to AC adverse effects and the possibility of additional AC medications may augment the consequences. In many situations, older adults see multiple physicians who prescribe multiple medications and to compound the problem they may not always go to the same pharmacy to get the prescriptions filled. Furthermore, the older adults may not tell their doctors about the other medications that they have been prescribed by another physician. This situation has the potential to lead to serious drug interactions and anticholinergic toxicity. The most common AC medications that older adults may forget to inform their healthcare professionals include antidepressants and first generation antihistamines (Kay et al, 2005B). First generation antihistamines include over-the-counter medications such as diphenhydramine, chlorpheniramine and promethazine that are commonly found in allergy, cold/flu, sleep and "PM" pain medications. Cognitive impairment is an important factor in determining the extent of AC burden and also increases the risk of receiving an AC medication (Lechevallier-Michael et al, 2004).

1.2.1.4 Determination of Anticholinergic Burden

Determination of AC activity has been around for several decades due to the numerous pesticides and chemical weapons that irreversibly inhibit acetylcholinesterase, thereby resulting in the

depletion of acetylcholine. Techniques for assessing AC activity are summarized in Table 2. Serum Anticholinergic Activity (SAA) radioreceptor assay is the laboratory assay that is the gold standard for measuring anticholinergic burden. This method is currently the most direct method of cumulative anticholinergic measurement, but is not practical in the clinical arena (Kolanowski et al, 2009). In this assay, AC medications and metabolites in serum are added to rat brain homogenate and competitively inhibit the binding of radiolabelled 3H- quinnuclidinyl benzilate (3H-QNB), a cholinergic agonist. 3H-QNB binds with high affinity to all of the muscarinic receptor subtypes. The amount of 3H-QNB displaced is used to quantify the cumulative amount of AC activity (Nebes et al, 2007).

Table 2: Methods of Burden Determination

Method	Year	Basis	Rating Scale	Calculation	Evidence	Practical in Clinical Setting
Serum Anticholinergic Activity (SAA)	1970's	Radio-receptor Binding Assay	n/a	Amount of 3H-QNB displaced	Gold Standard	No
Anticholinergic Burden Scale (ABS)	2002	Atlas of Psychiatric Pharmacotherapy	0-5	sum of all drug scores	AC burden significantly associated with falls	Yes
Anticholinergic Drug Scale (ADS)	2006	SAA	0-3	sum of all drug scores	AC burden associated with SAA values	Yes
Anticholinergic Rating Score (ARS)	2008	Expert based; disassociation constant for cholinergic receptor, rate of AC adverse events, and the literature	0-3	sum of all drug scores	ARS score was associated with an increased risk of anticholinergic adverse effects	Yes
Clinician Rated Anticholinergic	2008	Expert based; reported AC	0-3	sum of all drug scores	AC burden was significantly associated with	Yes

Method	Year	Basis	Rating Scale	Calculation	Evidence	Practical in Clinical Setting
Scale		activity			decreased executive functioning and increased memory impairment	
Anticholinergic Cognitive Burden (ACB)	2009	Expert-based; severity of drug's AC activity on cognition using a scale based on the literature between 1997 and 2007	0-3	sum of all drug scores	AC burden not associated with engagement or mental status	Yes
Drug Burden Index (DBI)	2009	FDA Approved doses	n/a	[(sum of daily doses)/ (sum of daily doses + min efficacious daily doses)]	AC burden was associated with worsening function using gait speed and grip strength	Yes/No

The binding is expressed in atropine equivalents, with higher atropine equivalents conveying a greater likelihood of AC properties of drugs and metabolites in serum (Nishtala et al, 2009). Research has shown that the use of SAA is an appropriate method to calculate AC burden in older adults. In a study of community-based elderly aged 70+, SAA was associated with the Mini-Mental State Exam (MMSE) scores. Those who had SAA levels in the 90th percentile and greater were 13 times more likely to have MMSE scores that were less than 24/30 compared to subjects who had no measurable SAA. Even low SAA was associated with cognitive impairment (Kay et al, 2005A; Mulsant et al, 2003).

The assay does have limitations however. Serum is not always representative of what is occurring in the brain. Plaschke et al investigated this relationship between AC activity in the cerebral spinal fluid (CSF) and blood. A competitive radioreceptor binding assay was used. They found that mean AC levels in the blood were 2.4 ± 1.7 pmol/mL and 5.9 ± 2.1 pmol/mL atropine equivalents in the CSF. AC activity was found to be 2.5-fold higher in the CSF. There was a significant linear correlation between blood and CSF levels. Therefore, it was determined that SAA does reflect central anticholinergic activity (Brecht et al, 2007). Furthermore, SAA does not appear to be affected by surgery or clinical care (Brecht et al, 2007). Contrary to these results, Mach et al found that SAA was elevated in patients who were delirious compared to those who were not (Mach et al, 1995). Therefore SAA may be affected by acute illness. Also, SAA is a tool that may be used to assess delirium. A study by Flacker et al. used a radioreceptor assay to assess delirium in 67 patients. They found that delirium was associated with higher SAA and there were a higher number of delirium symptoms associated with a higher SAA (Flacker et al, 1998). Other studies have used SAA to investigate the association of AC burden with functional outcomes. In the study by Nebes et al, participants were divided into low,

medium, and high SAA groups (Nebes et al, 2007). Participants underwent a walking assessment in which they had to walk a 15-foot course on carpet. Response time was assessed by pressing a button when they saw a one centimeter dot appear on a computer screen. After controlling for sex and age, the high SAA group (>1.9 pmol/mL) had significantly slower walk times and response times. It is suggested that the psychomotor slowing that occurs at high SAA levels may predict balance issues and falls (Nebes et al, 2007). Furthermore, several studies have shown the association between SAA and adverse CNS effects (Nishtala et al, 2009). This includes a study by Chew et al who used SAA to measure AC activity of the 107 most frequently dispensed medications used by older adults in long term care (Chew et al, 2008). Pharmacokinetic data was used to estimate the dose and AC activity relationship. The investigation found that 39 of the 107 medications showed detectable AC activity. Medications found to have a high AC activity, which was determined as a concentration of greater than 15 pmol/mL atropine equivalents, included amitriptyline, doxepin, clozapine, thioridazine, atropine, dicyclomine, L-hyoscyamine, and tolterodine. All 13 of the drug classifications evaluated had at least one drug that had AC activity at its therapeutic dose (Chew et al, 2008). While SAA is an appropriate way of determining AC burden, it is not the most practical in clinical settings. This laboratory assay is lengthy and requires a blood sample. This may prove difficult in older adults, especially those with dementia. Moreover, SAA cannot be readily performed in nursing homes, assisted living facilities and other locations where a calculation of burden would be helpful to prevent negative drug consequences because the assay is not widely available in commercial clinical laboratories.

Recently, several rating scales to assess burden in an efficient way have been developed. One such scale is the Anticholinergic Burden Score (ABS). The ABS is an additive score based on

quantitated AC effect of each psychotropic compound a patient receives. This quantitated AC effect is rated on a scale of 0 (no AC effect) to 5 (highly AC effect) based on information published in the "Atlas of psychiatric pharmacotherapy" (Shiloh et al, 1999). For example a medication such as amitriptyline has a value of 5 and risperidone or fluoxetine is a 1. In a study by Aizenberg et al, ABS was used to evaluate the effect of AC burden on falls. The ABS for each of the 102 patients was calculated. There were 34 patients who had a recorded fall and the ABS was calculated on this day. The mean ABS score for all of the patients was 2.68 ± 1.8 and for those patients that suffered falls was 3.25 ± 2.2. This value was significantly different from those who did not suffer a fall. This scale does not take the dose or dosing regimen into account. In addition, the basis for the rating scale is from a book and on the pharmacological mechanism of action (Aizenberg et al, 2002). Additionally, the referenced version of the text was not available. Therefore, the method of how the quantitated AC effect was determined was not understood.

Another scale is the clinician-rated anticholinergic score. This scale is different from the previous one in that it incorporates expert opinion. This scale was originally developed to assess potential effects of AC medication use on the severity of delirium symptoms. Scores range from 0, no effect, to 3, strong effect. The rating procedure and resultant AC drug list were based on the Summer's Drug Risk Number (DRN), where 62 medications were classified as 0 to 3. This was published in 1978. To update the list, 340 medications with reported AC activity as well as those used in the study population from the Han et al study in 2001 were included. Then 3 geriatricians independently rated the AC effect of each medication from 0 to 3 based on their clinical experience, knowledge of the properties of the drugs and the American Hospital

Formulary Service system. The median of the 3 ratings were adopted. All medications were counted, both AC and non-AC, in this method. Previous studies have shown that this rating scale has good criterion and predictive validity with the SAA. There were 544 participants enrolled in the Han et al. study, of which 342 or 62.9% used AC medications (Han et al, 2008). The study evaluated the longitudinal effect of cumulative AC drugs on memory and executive functioning. The mean clinician-rated AC score was 1.3 ± 1.5 for all 342 participants. The most frequently used medications that had a score of 2 or 3 included ranitidine, amitriptyline and fexofenadine. AC burden was significantly associated with decreased executive functioning and increased memory impairment (Han et al, 2008).

An additional scale was developed by Rudolph et al to assess the risk of adverse drug events (ADE) caused by AC medications. ADEs included central effects such as falls, dizziness, and confusion and peripheral effects such as dry mouth, dry eyes, and constipation. The Anticholinergic Risk Scale (ARS) ranks medications with AC potential on a scale of 0, limited or no AC potential, to 3, very strong AC potential. This rating scale is similar to the clinician-rated AC scale in terms of the scoring and the use of experts. Specifically, geriatricians and geriatric pharmacists determined the rank of each AC drug. These experts reviewed the disassociation constant for the cholinergic receptor, rate of AC adverse events, and the medical literature for the most prescribed medications (Rudolph et al, 2008). Rudolph et al. conducted a two part study; the first was a retrospective review of medical records for AC adverse effects and for medications included on the ARS. The second part was a medication reconciliation and review of the documented AC adverse effects. The study found that a higher ARS score was associated with an increased risk of AC adverse effects for both cohorts (Rudolph et al, 2008).

The Anticholinergic Cognitive Burden (ACB) Scale is the third scale that is based on evidence in the literature and expert clinician input (Kolanowski et al, 2009). Additionally, it has a focus on central AC effects only. It is an expert-based index that classifies the severity of a drug's AC activity on cognition using a scale that is based on a review of the literature between 1997 and 2007. Specifically studies that measured the AC activity of drugs and their cognitive effects were reviewed. The collected list of medications were then reviewed by an expert interdisciplinary team and categorized as mild, moderate, or severe. These three ratings were then translated to 1, 2, and 3. Total ACB was calculated by summing the ACB scores of all scheduled drugs prescribed for an individual. The study by Kolanowski et al. used this method to determine the association of AC burden and engagement in activity in nursing home residents (Kolanowski et al, 2009). The study found that 81.6% of the Pennsylvania nursing home patients took at least 1 AC drug. Additionally, 56.3% were prescribed two or more AC drugs. There were a total of 28 AC medications that the patients were taking with furosemide and metoprolol as the most commonly prescribed. The authors concluded that decreased mental status was associated with engagement outcomes, but AC burden scores were not (Kolanowski et al, 2009).

Carnahan et al also developed a rating scale, the Anticholinergic Drug Scale (ADS), using ratings of 0 to 3, with level 0 = no known AC properties; level 1 = potentially AC as evidenced by receptor binding studies; level 2 = AC adverse events sometimes noted, usually at excessive doses; and level 3 = markedly AC (Carnahan et al, 2004). This quantification of AC burden was found to be significantly associated with SAA. Their study also supported the separation of ACs into categories based on AC potency. Overall, the findings of Carnahan et al suggest that ADS may be a tool for assessing AC burden (Carnahan et al, 2004). This tool is unique in that it

includes both as needed medications, PRN, and scheduled. In addition, the authors replicated the study, but with modifications to evaluate the association with SAA. The modifications included adjusting for dose. The maximum recommended daily dose for each medication on the list was determined using the product labeling approved by the Food and Drug Administration. The maximum dose was compared to the dose that the participants were taking. Weights were applied to the participant's dose and ranged from 1 to 4. For instance, if the dose was less than a third of the maximum then it was weighted as 1 and if it was greater than the maximum recommended daily dose then it was weighted as 4. With this modification, the analyses found a significant association with SAA, but not significant compared to the non-modified scale (Carnahan et al, 2006). While not significant in this study, dosing still explained more of the variation seen by the model than by not including it. Furthermore, dosing is important in calculating burden as a higher dose leads to more exposure and a greater level of AC activity.

The last and most recent scale is the Drug Burden Index (DBI). The DBI measures overall exposure to medications with AC and sedative properties. This scale includes the daily dose of the AC medications and the minimum efficacious daily dose approved by the FDA. The total drug burden is equal to the sum of the daily dose for a medication divided by the sum of the minimum efficacious daily dose and the daily dose, for both sedatives and ACs. All medications, except topical ones without significant systemic effects were included. In the study by Hilmer et al, the index was used to evaluate the relationship between physical and cognitive performance and medication use (Hilmer et al, 2009). The study found that higher drug burden was associated with worsening function using gait speed and grip strength. Moreover, a one unit increase in the DBI predicted a significant decrease in gait speed of 0.04 m/s, which is more significant than the additional decline in physical or mental comorbidity (Hilmer et al, 2009).

While the use of laboratory measurements that measure AC activity in the CSF is the best followed by a tool such as SAA, it is not practical in most clinical settings. In addition, it is not only time-consuming but also expensive. Furthermore, alternative methods such as the use of one of the many scales may be more appropriate for special populations such as patients with dementia. All of the scales except for the DBI do not take into consideration of the dose. Additionally, only the ABS and the DBI do not use a 0/1-3 scale to categorize the medications. While the DBI has significant benefits over the other scales as it takes into consideration the dose, it is more difficult and time-consuming compared to the other scales. Therefore it may not be entirely practical in a busy long-term care or hospital setting. When the other scales are compared against each other, the ABS is advantageous as it provides a wider scale in which to categorize drugs (0-5), but its basis is a textbook. The Clinician Rated Anticholinergic Scale and the ARS are almost identical. The ACB is different by including only those with central effects, this a disadvantage compared to the others. The ADS is older compared to the other scales except for the ABS, and is based on the SAA, which while it is an imperfect measurement, it is still better than using expert opinion alone or not including AC potency as a component of burden measurement.

1.2.2 Prevalence of Use

Several studies have shown that older adults are at greater risk of developing negative side effects from prescribed and over the counter medications that have AC properties. Furthermore, in some cases these side effects may be attributed to worsening dementia or the increase risk of cognitive impairment, falls and functional decline (Robinson et al, 2009; Han et al, 2008). These negative cognitive effects include impairment in working memory, episodic memory, processing

speed and praxis. Moreover, use of AC medications is a significant predictor of overall performance on general activities, mild cognitive impairment and delirium (Chew et al, 2008). It is important to note that AC drugs have both central as well as peripheral side effects, including confusion, sedation, loss of concentration, hallucinations, and delirium. In older adults with dementia these effects may be magnified (Modi et al, 2009). Older adults are more likely to have multiple chronic diseases and therefore receive multiple medications. Also, there is an increasing trend of drug usage in older adults, even without the addition of chronic diseases (Han et al, 2008). In many cases more than one AC medication is prescribed to the same older adult. Also, they are more likely to receive a medication with AC effects. Studies for decades have shown that older adults receive a large number of medications with AC effects. A summary of the prevalence studies is provided in Table 3. A study in 1983 found that approximately 60% of nursing home patients and 40% of ambulatory patients received a medication with AC properties (Feinberg, 1993). More recent studies have indicated that as many as 27% of community dwelling adults are using AC medications (Merchant et al, 2009). Furthermore, a study by Han et al. found that more than 30% of nursing home residents take two or more AC drugs and estimated that this number was closer to 50% in the general population (Han et al, 2008). Another study in France found that the 327 older adults who were continuous AC users had poorer performance on cognitive tests at 1 year than non-users (Ancelin et al, 2006). In the study by Han et al, 342 (62.9%) of 544 subjects were using AC medications. The number of subjects using these medications increased to 364 and 378 in the following years. The mean AC score was 1.3 ± 1.5 and a median of 1.0. The most commonly used AC medications had moderate to strong effects. These included ranitidine, amitriptyline, fexofenadine, nortriptyline, and paroxetine (Han et al, 2008).

Table 3: Summary of Prevalence Studies		
Author; Year	**Population**	**Result**
Blazer 2nd et al; 1983	5,902 nursing home residents and 5, 861 ambulatory subjects of Tennessee Medicaid recipients ≥ 65 YO	59% of nursing home residents and 23% of ambulatory subjects received at least 1 AC drug
Lechevallier-Michael et al.; 2004	1780 subjects aged 70 and older, living at home in South western France	13.7% of the subjects used at least one drug with AC properties
Ness et al; 2006	532 patients from the Iowa City VAMC	27.1% used at least 1 AC drug
Johnell et al; 2007	732,228 adults ≥75 YO from the Swedish Prescribed Drug Register	6% were prescribed AC drugs
Han et al; 2008	544 community dwelling men ≥ 65 YO with diagnosis of hypertension	62.9% were using AC medications
Lakey et al.; 2009	174 recipients of home health services in Eastern Washington State	80.0% were using a medication with AC effects; 66.1% were using weak AC and 33.8% potent agents
Olsson et al.; 2010	3705 residents in nursing homes and special dementia units in a Swedish county	20.7% in nursing home used AC drugs; 18.5% in dementia units.
Kumpula et al.; 2010	1004 residents of a Helsinki, Finland long-term care ward in 2003	36% mild AC burden (ARS score = 1-2); 19% high AC burden (ARS score ≥ 3)

In addition, Blazer et al. in 1983 determined in their study that between 21% and 32% of elderly patients living in nursing homes were using two or more AC drugs. Ten to 17% of nursing home residents were using > 3 ACs and up to 5% of nursing home residents were using > 5 ACs. Regarding combination medication formulations, the most frequently used combinations included thioridazine/benzhexol and thioridazine/chlorpromazine (benzhexol is rarely used now). Also, the use of thiordiazine concomitantly with amitriptyline was prevalent, which may signify that there was a lack of alarm on the part of the prescribers and other involved healthcare professionals about the overall summation of AC effects. One study found that by administering AC medications, delirium could be induced and then reversed by administering cholinergic agonists (Han et al, 2008). Similarly, Spore et al. determined that 43% of elderly patients in nursing homes were taking psychotropics (Mintzer et al, 2000). Studies suggest that drugs with AC effects may reduce the effectiveness of AChEIs when they are taken together (Carnahan et al, 2002). In addition, the combined use has the potential to increase the rate of cognitive decline in patients and affect the severity of delirium symptoms that may be present. In dementia and AD, AC medications are prescribed for the treatment of comorbid conditions associated with dementia. In addition, they may also be used to treat the side effects of AChEIs in a prescribing cascade. Studies have shown that the concomitant use of AChEIs and AC medications is not uncommon. A study by Roe and colleagues found that older adults with probable dementia were more likely to use moderate to strong AC medications compared to matched controls (Roe et al, 2002). In addition, Carnahan and colleagues measured the prevalence of AC use in Iowa Medicaid beneficiaries over the age of 50 who were on AChEIs. They also evaluated the change in use of the ACs when an AChEI was started. They found that approximately 36% of the patients were using both classes at the same time. In addition, about

75% of the AC medications were considered highly AC with known adverse events associated. The incidence of AC use when an AChEI was started increased in the study participants (Carnahan et al, 2004). Another study found that 1/3 of community dwelling older adults with dementia were taking AChEIs and AC medications concomitantly. Modi et al in 2004 found that 46.7% of the Indiana Medicaid population was taking the two classes together. Furthermore, of this concurrent population, 58.1% were taking a medication classified as markedly AC. H2 antagonists, respiratory antihistamines and urinary antispasmodics were the three most commonly prescribed AC medication classes (Nebes et al, 2007). Other studies have shown that older adults with dementia are at an increased risk of the receiving an AC medication (Gill et al, 2005).

It is suggested that the cause for this phenomenon is the side effects associated with AChEIs and comorbid conditions associated with AD. Older, less expensive drugs are more likely to be prescribed due to economic reasons or prescription biases. The older, less expensive drugs include tricyclic antidepressants which are known to have high AC effects (Inouye, 1999). Roe and colleagues concluded that based on the potential for antagonism between AChEIs and AC medications that even short-term use is contraindicated (Roe et al, 2002). Interestingly enough, trials for donepezil, rivastigmine and galantamine did not allow participants to be on AC medications. Determining whether a patient will develop or experience adverse effects to AC medications depends on several factors including total AC load, cognitive functioning, and individual pharmacokinetic and pharmacodynamic variability (Roe et al, 2002). There is some evidence in the literature about the effects of concurrent use. In one study, 69 AD patients taking AChEIs and AC meds chronically had greater cognitive decline at 2 years than those not taking ACs (Han et al, 2008). There is some evidence that the concomitant use of AChEIs and AC

medications may decrease the effectiveness of AChEIs. Even with this preliminary evidence it is not uncommon for the two medication classes to be prescribed together (Modi et al, 2009).

In addition, to being more likely to receive an AC medication, the demented population is more likely to suffer from adverse events and reactions due to AC medications (Thienhaus et al, 1990). It is suggested that demented patients are significantly more vulnerable than non-demented in cognitive effects of AC medications, possibly due to the central cholinergic deficiency (Doraswamy et al, 2006). In addition, studies have shown that the risk of adverse cognitive effects increases with total AC burden or load and that these medications have the potential to worsen symptoms (Roe et al, 2002; Tune et al, 2003). It is possible for a dementia patient to suffer from AC toxicity, which is characterized by signs and symptoms of dysfunction of the parasympathetic system and the brain. These signs and symptoms include decreased attention span, disorientation, psychotic features and psychomotor agitation. All of these symptoms can lead to functional impairment (Thienhaus et al, 1990). In a study by Thienhaus et al, demented participants displayed significant impairment in association with higher AC serum activities compared to non-demented patients (Thienhaus et al, 1990). The AC serum levels that were associated with significant deterioration of selected cognitive functions caused no dysfunction in the 18 non-demented subjects. Measures of recognition, concentration and retrieval of information (corresponds to deterioration of knowledge memory) all decreased significantly with higher AC serum levels (Thienhaus et al, 1990). Other studies have shown worsening performance on reaction time, attention, face and narrative recall, and visospatial and language abilities (Doraiswamy et al, 2006). A study by Jewart et al. showed that when dementia patients were taken off AC medications, specifically incontinence medications, they demonstrated better performance on tests of mental status and behavior (Jewart et al, 2005).

1.2.3 Outcomes of Use in Older Adults

There are over 600 medications that have AC properties (Tune et al, 1999), some with intended effects and others that are unintended. Furthermore, Tune et al. tried to determine serum AC activity of the 25 most frequently used drugs in the elderly. They found that 14 of the total 25 drugs had some level of AC activity. Ten of these drugs, which included ranitidine, codeine, dipyridamole, warfarin, isosorbide, theophylline, nifedipine, digoxin, and prednisolone, caused significant impairment in recent memory and attention in psychiatrically healthy elderly subjects (Tune et al, 1992). Often times, several ACs were given concurrently (Mintzer et al, 2000; Tune et al, 1992). Scopolamine is strongly AC and it is suggested that it specifically targets muscarinic receptors. Other medications such as the antibiotic piperacillin, has unintended AC effects. According to the package insert, piperacillin is a bactericidal drug that works by inhibiting septum formation and cell wall synthesis of bacteria (Zosyn Package Insert, 2009). The package insert does not include the AC properties of this medication. Yet, validated laboratory assays, such as the serum anticholinergic activity assay, SAA, have ascertained that this is the case (Mintzer et al, 2000; Tune et al, 1999). This assay has been shown to be a better predictor of cognitive impairment than age or the total number of drugs that a person takes (Chew et al, 2008). The lack of knowledge about the AC properties of medications may be due to insufficient information about how most prescription and over-the-counter drugs as well as their metabolites affect the cholinergic system. Therefore, just knowing a medication has AC properties does not provide the full picture (Chew et al, 2008). Overactive bladder is a good example of this situation. It is a disease state that is common in older adults with dementia, with some estimates as high as 53%. Other reports place this number between 11% and 90% depending on the methods of estimation and the definition of urinary incontinence (Yap et al,

2006). Much of the incontinence in dementia is functional, which refers to incontinence associated with physical disabilities, external obstacles or mental disabilities. Antimuscarinic medications are the pharmacological treatment for overactive bladder. These agents work by blocking the effects of acetylcholine at muscarinic receptors, specifically of the bladder. Hence, there is a reduction in the frequency and intensity of involuntary detrusor contractions. Research has shown that the M2 and M3 subtypes are located within the detrusor muscle, specifically the M2 receptor predominates with a 3 to 1 ratio. Furthermore, it is the M3 subtype that is mostly responsible for muscle contraction. While the specific action of these antimuscarinic agents is to target the M3 receptors, they have the potential to bind to all of the muscarinic receptors, including M2 and M1. Therefore, they have the potential to cause adverse events. In addition, they have the potential to worsen or negatively impact chronic diseases. There are reports and evidence in the literature of memory loss, confusion and delirium with the use of non-selective muscarinic receptor antagonists (Kay et al, 2005A). Furthermore, these neuropsychiatric adverse events may be underreported as they may be considered part of normal aging (Kay et al, 2005A).

1.2.4 Outcomes of Use in Dementia

In dementia patients AC toxicity can result in morbidity and mortality, behavioral symptoms and delirium. Studies have found correlations between serum AC levels and functional disability, agitation and delirium (Carriere et al, 2009). Delirium and confusional states are common in dementia and associated with mortality rates up to 40%. In terms of cost, delirium is estimated to account for more than $32 to $152 billion each year, according to a 2008 study (Leslie et al, 2008). In addition, there are costs for increased hospital stays, nursing home placement,

rehabilitation services and home health care (Inouye, 1999). Dementia is one of the strongest risk factors for the development of delirium. In addition, the severity of the dementia correlates to the risk for delirium. However, detection of delirium in dementia is only in about 12% to 31% of all cases. It is also known that patients with dementia have a significantly longer episode of delirium compared to those who do not have dementia (Lim et al, 2006). One study showed that approximately 40-50% of patients with dementia had persistent delirium for 6 to 12 months (McCusker et al, 2003). Delirium and dementia are both associated with cholinergic disturbances, but the difference is that delirium is an acute condition that may occur if a person has dementia (Tune, 2001). There are three types of delirium: hyperactive, hypoactive and mixed delirium. The first and third are often associated with cholinergic toxicity. Some studies suggest that up to 11.5% to 39% of all delirium in AD patients is due to medications. Medications that are known commonly to cause delirium include high dose narcotics, benzodiazepines and ACs. In addition, to the medications listed above, lithium has been linked to delirium in dementia patients (Alagiakrishnan et al, 2004). Other outcomes reported in studies include falls and geriatric syndromes (Tune et al, 1999). Therefore, the use of AC medications with AChEIs in patients with AD has the potential for serious negative outcomes and may decrease overall effectiveness of AChEIs.

1.3 Barriers to Research Participation in Alzheimer's Disease Studies

The research that has been conducted and continues to be conducted in this area is mostly observational. According to the current standards, a randomized controlled interventional study to reduce AC burden would provide a more definitive conclusion on the impact of AC burden on dementia patients. One reason that these studies have been difficult to perform is patient

recruitment. Recruiting patients is a difficult process and there are many barriers that need to be overcome for this to occur. This section will discuss the barriers associated with recruiting older adults to participate in clinical studies.

Several studies have documented that older patients are underrepresented in clinical research. There are a growing number of older adults in the population, which represents a serious dilemma for translating research into clinical practice (Marcantonio et al, 2008). This is apparent in Alzheimer's research as well. Unfortunately, recruiting any sample of older adults, especially AD participants, into clinical research is difficult, time consuming, and expensive. Some studies have investigated the reasons behind low participation and found that older adults who refuse to participate in research tend to be male, to be older, and belong to a lower income group (Arean et al, 1996). This is true for AD studies as well. In a 1997 study by Schneider and colleagues the entry criteria for industry sponsored AD clinical trials preferentially selected wealthier, more educated and white individuals (Olin et al, 2002). Research has also identified several barriers that exist to older adult and Alzheimer's disease participation in research, but population size and availability are not issues. Barriers can be divided into universal, minority, and researcher specific.

1.3.1 Universal Barriers

There are many universal barriers including spousal support, location, transportation, caregivers, the design of the research project, and knowledge of the study. Universal barriers include lack of spousal support. Interviews show that if the spouse does not approve of the study or the research than the possible participant will not volunteer. Approximately 55% of potential participants indicated that they would decline if their spouse was not interested or did not approve

(Marcantonio et al, 2008). For minorities, not involving the family or the spouse in the study and the recruiting process may lead to fear and distrust of the research. Research has shown that as many as 32% of potential participants refused to participate in research because their families and physicians discouraged them (Arean et al, 1996). Another barrier is location and transportation, traveling to a hospital or a place that is not a residence may lead to a participant declining. In a study by Marcantonio et al in 2008, 98% of the 50 older adults surveyed declined participation in a study if they had to go to a hospital (Marcantonio et al, 2008). For some participants the research projects may not be held in communities where they live. Physical limitations such as disabilities and health concerns as well as living in unsafe areas may preclude participation. It is well known that older adults tend to have more health problems and be disabled compared to younger counterparts. In addition, those with dementia are more likely to have other comorbid conditions and require other transportation. Also, many settings may not be ideal as participants may not want their friends and families to know that they are participating in research or that they have a specific condition. In a 1993 study by Arean et al, 99% of the referrals from a senior center preferred participating in a university setting because they were afraid that their friends would find out (Gelman, 2010). Another factor is care-giving, in which some older adults may be caregivers from their own aging parents, spouses, or children. This may hinder their ability to take time to travel to a hospital site or even afford transportation (Marcantonio et al, 2008). In addition, Marcantonio and colleagues found that type of research also plays a role. Research that involves an invasive procedure is less likely to acquire participation. Of the 50 participants interviewed 61% declined if a lumbar puncture was included (Arean et al, 1996). Even more basic than the type of research is knowledge about the project. Many potential participants may not even be aware of the opportunities for research. Advertising

in older adult specialty newspapers or in local senior centers may be a useful method. Enlisting the help of physicians and other healthcare professionals may also be useful. For minorities, having a community leader that they trust disseminate the information about the study or translating the advertisements in native languages may overcome this barrier. Another common barrier is a long study period. A study that requires multiple visits or has a long duration will dissuade possible participants. The desire to "be around" when the results are published or shared is very important. There is some thought that the longer the duration of the study, the less likely that they will be around for it (Marcantonio et al, 2008), (Arean et al, 1996). Other barriers to research, especially AD research, include caregiver stress, denial that there is a need for help, view that reimbursement is not worth it, multiple diseases and limited functional abilities, denial of vulnerability, lack of personal benefit and fear of adverse reactions (Souder et al, 2007). In addition, distrust of research, lack of confidentiality, fear of safety, schedule conflicts, poor access to medical care, and lack of knowledge were identified by UyBico et al in 2007. Lastly, many older adults may not consider participating in research a worthwhile expenditure of energy and time when they are already burdened with multiple stressors (Arean et al, 2003).

1.3.2 Race and Minority Barriers

Race and minority status is a controversial barrier to participating in research. While many studies have identified Hispanic and Black individuals with AD as an underrepresented group that faces many barriers to participating in research, other studies have found that belonging to an ethnic group was not significantly related to responding to or dropping out of research. Arean and colleagues pointed out that while these studies have not found a difference in the rates of

participation in research among ethnic groups, the reasons for not participating, and therefore the recruitment and retention strategies, do differ considerably between ethnic-minority and non-Hispanic white older adults (Arean et al, 1996). The one issue that is well understood is that recruiting and retaining older minorities is much more complex than non-Hispanic whites. The main barrier is centered on enthocultural beliefs, specifically beliefs of mental illness, help-seeking behaviors, and socioeconomic status. This barrier may manifest as fear and distrust, transportation issues, lack of information about the disorder, negative cultural attitudes toward AD and mental illness in general, and lack of knowledge about the benefits of participating (Marcantonio et al, 2008). One issue that was mentioned above is the language barrier, especially for Hispanics and other minorities. A significant proportion of the current Hispanic AD population are not fluent in English. However, many clinical trial sites lack Spanish-speaking staff, and many clinical trials lack materials in Spanish (Olin et al, 2002). Transportation issues are universal, but one specific concern is a fear of potentially becoming a victim of racially motivated crimes. Therefore many older minorities may be less motivated to visit a center or location that is not within their neighborhood. Care-giving is a common situation for many minorities and may prevent the caregivers to participate in research. Studies have shown that many African American women have custody of their grandchildren and have to meet the needs for these children as well as care for their own needs. These issues often resulted in participants' having difficulty in coming to treatment and coming for follow-up interviews (Marcantonio et al, 2008). Education or information about the disorder is not a problem that affects just minorities, but it is more common in this population. Studies have found that many older adults are willing to participate in research studies but do not do so because they know little about the disorder under investigation and of the possible benefits to participating in

research (Marcantonio et al, 2008). Low literacy and lack of contacts with the medical system contribute to low rates of participation, in addition, to delays in seeking medical attention. Therefore, if a family is not seeking medical attention then they will unlikely know about research opportunities and in many cases be excluded due to advance disease by the time diagnosis is made (Souder et al, 2009). Low education and cultural factors lead to misguided views of AD and mental illness. For some minorities they view these disorders as a multidimensional condition, consisting of religious, spiritual and environmental aspects. Therefore, attempting to treat it in following western guidelines may appear to be degrading and decrease minority participation (Souder et al, 2009). Cultural competence is one of the most important issues to consider when conducting research with minorities. Research has shown that efforts to recruit minorities without taking into consideration cultural factors can lead to failed projects. It is well known that minorities are more likely to have stereotyped ideas about mental health problems. Therefore, they are less likely to participate in research. These stereotyped ideas about AD and other mental illnesses lead to associated stigmas and participant burden. Stigma concerns of older minorities are different from their White counterparts. Many older minorities are concerned with the impact a psychiatric diagnosis will have on the family's reputation (Souder et al, 2009). In addition, minorities have a tendency to view themselves as sicker compared to their non-Hispanic White counterparts. This perceived level of health and disability significantly influences participation in research (Marcantonio et al, 2008), (Arean et al, 2003). For Blacks, cultural attitudes may dictate that they cope with illnesses by taking care of their relative within the family and social network, instead of using the medical community. These beliefs also lead to a view that AD or other diseases are normal and natural occurrences (Souder et al, 2009). Fear is another barrier that is not unique to minorities, but it appears

differently in this population. Fear leads to mistrust of science and health services. For various immigrant groups this fear stems from war related atrocities that were conducted in the name of science. In Blacks, the most significant barrier to participation stems from historical events, such as the infamous Tuskegee Syphilis Study. These events have lead to the perception that they are treated differently by medical professionals than their White counterparts due to their race. Whether this is real or perceived racism, it still affects participation in research (Souder et al, 2009). The recruitment of special populations requires increased resources and time to develop trust, knowledge of the culture, engagement of the community, and special strategies targeted to the particular needs of the group. Inability to recruit a sufficient number of participants is a major reason for failures in clinical trials (Buckwalter, 2009).

1.3.3 Researcher Related Barriers

Researchers face many barriers to recruiting potential older adult AD patients as indicated above. Overcoming participant views, attitudes and perceptions are important, but not the only barriers faced when recruiting patients. Other obstacles include health information regulations, physician and healthcare practitioner barriers, economic concerns and study design. HIPAA, Health Insurance Portability and Accountability Act, changed the way recruitment was handled by all researchers. This regulation, specifically the Privacy Rule, took effect in 2003. This required researchers to gain information about patients from a "covered entity," specifically a health care provider, health plan, or clearinghouse with access to the patient's personal health information (PHI). What this meant was that a health care provider had to identify potential participants and ask them for written permission to give the researcher their name and phone number if they want to learn more about a study. As a result, study recruitment is much more difficult (Sullivan-

Bolyai et al, 2007). Other barriers that stem from this regulation include "work burden." Work burden refers to working with busy clinicians to assist in recruitment. It is well known that physicians and health care providers are extremely busy and have a large workload. Adding an additional responsibility to this load can be very difficult and typically research ends up at the bottom of the to-do-list. In some cases research may be viewed as extra work without compensation or perceived as taking time away from providing patient care (Sullivan-Bolyai et al, 2007). In addition, research may be viewed as a financial disincentive if it diminishes clinic profit by reducing the number of patients that can be seen. As mentioned above, physician and health care provider bias towards the research can impact the willingness to participate by the patient. The desire to protect their patients can also restrict patients' rights and decision making opportunities. A study by van Ryn and Burke (2000) found that physicians' perceptions of patients may influence whether they recommend the research (Sullivan-Bolyai et al, 2007). These perceptions are influenced by the patients' race and socioeconomic status. For instance, physicians rated patients who were African American as less compliant. Health care providers may be wary if they perceive a study could physically harm or put undue stress on their patients (Sullivan-Bolyai et al, 2007). Other hurdles include competing service demands on the provider, multicultural differences, lack of knowledge, bias against research leading to inactive recruitment, overly restrictive eligibility criteria, complex IRB requirements, poor relationships with the research team – leading to distrust of researchers and their motives, dislike of the research procedures (Buckwalter, 2009; UyBico et al, 2007).

The literature illustrates that there are many barriers to conducting research in the older adult population, specifically the AD population. There are many ways to overcome these barriers,

but they are both time consuming and expensive. In addition, it is not always possible to improve participant recruitment even if obstacles have been removed.

1.4 Chapter Summary

In this section a detailed summary of AD was provided including current treatments. ChEIs, the current symptomatic treatment, has a pharmacological interaction with other medications, specifically those with AC properties. Medications with AC properties are numerous and there is much evidence that they cause negative outcomes in older adults. There is also some evidence that they may cause negative outcomes in dementia patients. Additionally, the idea of AC burden, the cumulative effect of the total AC medications that a person consumes, was introduced and measurements of this burden described. While research in this area is constantly increasing, most of the studies are observational. While a randomized controlled study would provide important evidence as to the causal relationship, recruitment issues are a considerable barrier to performing this type of research. Therefore the last section discusses the several barriers that are involved including universal, race/minority and researcher related ones. These barriers once taken into consideration and overcome will enable stronger studies to occur. In Chapter 3 the preliminary research that has been conducted will be discussed. Two preliminary projects are discussed, one that was completed and the other that was stopped due to low patient recruitment. In Chapter 4, the methodologies for a retrospective database project conducted at Piedmont Geriatric Hospital are described. Finally the results and the discussion are presented in Chapters 5 and 6, respectively.

Chapter 2

Significance and Specific Aims

2.0 Significance

AD and dementia in general are incurable diseases with no disease modifying treatments available. As the disease progresses, great medical and social changes occur. The cognitive deficits that develop limit patients' ability to understand written information and participate in consequential conversation. The limited social activities due to deficits in function may increase the risk of illnesses and poor health that may trigger negative behaviors and increase medication uses. Additionally, there are negative changes in behavior caused by the inability to articulate discomforts or frustration. Behavioral problems can increase the risk of receiving harmful medications (Forchetti, 2005). Working with moderate to severe dementia patients can be difficult, which may be one reason why there is little research in this population.

While most families prefer to keep their loved ones at home for as long as possible, many moderate to severe dementia patients live in long-term care facilities or hospitals. A 2008 study found that 68% of all nursing home residents had some degree of cognitive impairment (Alzheimer's Association 2010). Additionally, 41% of those older adults had moderate to severe impairment (Alzheimer's Association 2010). Therefore it is important to study dementia patients in institutionalized care.

The current standard of care with the use of cholinesterase inhibitors (ChEIs) and memantine, is very expensive and provides only modest improvements. Only ChEIs have an indication for mild disease, but both ChEIs and memantine have indications for moderate and late disease. While there are some studies that suggest positive outcomes from the use of these medications in late disease, there are also studies that show no significant outcomes (Forchetti, 2005). Furthermore, research has shown that receiving a cholinesterase inhibitor increases the likelihood of being prescribed an AC medication (Gill et al 2005; Robinson et al, 2009). Moreover, the concurrent use of the two classes of medications is not an uncommon occurrence (Feinberg, 1993). This combined use may reduce the benefit of the ChEIs as these two classes have opposing pharmacological mechanisms of action. There are epidemiological studies that show that concurrent use of these two classes has the potential to cause harm to AD patients (Han et al, 2008). The ChEI approval trials excluded AD patients taking AC drugs; therefore there is no evidence to support the concurrent use of these two classes of medications as part of FDA-regulated drug development.

Time is also a significant factor in dementia. Each dementia patient is different in how they progress through the disease. Some progress more rapidly than others and some have more behavioral or functional problems than others. By collecting data over a period of time, one is able to better understand and correlate the effects of medications and other factors on health and social outcomes. Therefore, research in dementia patients should consider change over time rather than a single point in time (Twisk, 2003).

This study is based on the hypothesis that drugs with AC effects impair function, memory, and behavior in dementia patients. Furthermore, the concurrent use of AC drugs with ChEIs impairs

the efficacy of drug therapy in patients taking ChEIs. While most studies focus on the cognitive effects of AC burden and concurrent use, few investigate functional and behavioral outcomes. It is believed that AC effects on dementia may lead to a faster decline in cognition, function, and behavior based on the evidence from the use in psychiatrically stable older adults (Tune et al, 1992) It is expected that this decline will be seen in the patients taking ChEIs as they are more likely to receive an AC drug and subsequently higher anticholinergic burden that would counteract the effects of ChEIs. Hence, the greater the burden it is expected the greater the decline in function, cognition, and behavior over time.

2.1 Specific Aims

The specific aims of this study are:

- To quantify anticholinergic burden in moderate to severe dementia patients receiving long term treatment in a state geriatric psychiatric hospital.
- To assess the function in dementia patients with varying anticholinergic burdens due to their concurrent medications.
- To assess the cognition and behavior in dementia patients with varying anticholinergic burdens due to their concurrent medications.
- To identify anticholinergic medication- and patient-related factors relevant to functional outcomes in dementia patients taking anticholinergic drugs.

Chapter 3

Preliminary Research

3.0 Chapter Introduction

In this chapter two preliminary studies investigating AC use will be discussed. The first study is a retrospective analysis of the University Health-System Consortium database, investigating the prevalence of AC drug use in older adult inpatients without dementia. This study is still ongoing, therefore only preliminary results are provided. The second study was a prospective analysis of functional, behavioral, and cognitive functioning in older adults with mild to moderate AD. This study was stopped prematurely due to the difficulties in recruitment of study participants.

3.1 Anticholinergic Drug Use in the Hospitalized Elderly

3.1.1 Background and Significance

AC medications inhibit or block the actions of acetylcholine in both the peripheral and the central nervous system. Wide varieties of medications possess AC properties and are frequently prescribed for health conditions common in the elderly. The medications can have a cumulative effect that may cause early cognitive declines (Kay et al, 2004). Older adults are vulnerable because of the decrease in effectiveness of the blood-brain barrier, changes in body composition and altered drug elimination pathways.

This in conjunction with reductions in metabolism and elimination increase the risk for adverse AC effects. The central nervous system dysfunction is shown by changes in memory, disruption of sleep, hallucinations, confusion and delirium that could lead to an increase in hospital stay (Kay et al, 2004).

The specific aims of this project were to study the prevalence of AC drug use in non-demented elderly inpatient population, to observe the most commonly used AC medications and to study the relationship between length of stay and AC burden. Based on the available evidence we hypothesized that the prevalence of AC drug use was common and that those patients taking these medications would have a longer length of stay.

3.1.2 Methods

3.1.2.1 Data Source

The data was obtained from the University Health-System Consortium (UHC) Clinical Database (CDB), which is an alliance of 90 academic health centers in the United States. The UHC CDB-Pharmacy database contains procedure and diagnosis-specific data from discharge abstract summaries, Universal Billing Code of 1992 (UB-92), and medication use data from charge transaction masters and patient billing files for all inpatients at participating centers. The UB-92 is a standardized database used by hospitals to generate itemized charges for patient visits. One year of data was evaluated from October 2003 to September 2004. This study was reviewed by the Virginia Commonwealth University (VCU) Office of Research Subject Protection Institutional Review Board (IRB) and found to qualify for exemption from federal regulations requiring IRB review and approval. The study population included hospitalized patients 65 years

of age or older with no evidence of dementia. Evidence for dementia included ICD-9 codes for any type of dementia illness or receiving a ChEI.

3.1.2.2 Data Collection

Several variables were collected from the database including the medications that a patient was receiving, age, sex, race, observed hospital length of stay (LOS), AC drugs, severity score (evaluation of severity of illness and risk of mortality), whether they were discharged to a nursing home and the presence of delirium based on ICD-9 codes. The ICD-9 codes included 292.81 (drug-induced delirium), 293.0 (acute delirium) and 293.1 (subacute delirium). Calculated variables included AC medication use, AC burden, and AC potency. The outcome variable, LOS, was not normally distributed and was log-transformed. AC medication use was coded as yes/no and was determined for each patient in each group. The AC medications with CNS activity included in this review are listed in Table 4. Combination drug products containing one of these ACH drugs were also evaluated. For each AC medication, AC burden was determined using the following equation: dose [high, med, low] x days of therapy x ACH potency [high, med, low]. These classifications as high, medium or low were based on clinical judgment (by a geriatric pharmacist and researcher) and dosing recommendations for the elderly obtained from Lexi-Comp®. The resulting values were summed across all AC drugs. AC potency was estimated based on published *in vivo* and *in vitro* data available in the published literature, Lexi-Comp and clinical judgment.

There were potential confounding variables including discharge status, race, sex, age, delirium, and severity score. Discharge status was coded as "yes" = 2 if discharged to a skilled nursing facility, rehabilitation center, psychiatric center, long-term care hospital, intermediate care

facility, federal hospital, acute care facility, or hospice/medical facility, otherwise it was coded as “no” = 1. Race was coded as “White” = 1, “Black” = 2, and “Asian”, “Hispanic”, “North American Indian/Eskimo” or “other” = 3. Sex was coded as “male” = 1 and “female” = 2. Delirium was coded as “yes” = 2 and “no” = 1. The UHC database accounts for severity of illness and comorbid conditions (CCS) variables using a combination of the Diagnosis-Related Groups (DRGs) and the UHC Complication Profiler (UCP) (UHC, 2008). Four levels of severity are defined: as baseline (no substantial CCS), moderate CCS, major CCS, and catastrophic CCS (surgery).

3.1.2.3 Data Analysis

The prevalence of centrally acting AC drug use was calculated by dividing the number of patients taking the drugs by the total number of patients in the non-demented group. The percentage use for each drug was calculated by dividing the number of courses of therapy for that drug by the total number of courses of therapy for all AC drugs. Average daily dose and average days of therapy for each of the centrally-acting AC drugs was also calculated.

Stepwise multiple linear regression was used to assess the relationship between LOS and the independent variables. LOS was log transformed for this analysis. The independent variables evaluated were standardized scores for age, race, sex, severity score, discharge status, whether or not delirium was documented, and whether or not the patient received an AC drug. Furthermore, this technique was also used to determine the relationship between LOS and AC burden in those patients who received at least one AC medication. This was performed to evaluate whether higher AC burden is associated with longer LOS in patients without dementia. Again the

dependent variable was log transformed LOS and the independent variables included were age, sex, race, severity score, discharge status, delirium diagnosis, and AC burden score.

3.1.3 Results

The results included in this section are preliminary as the study analysis is still continuing. There were a total of 210,103 inpatients in the dataset without dementia; of this group 37.8% or 79,493 were taking one of the medications listed in Table 4. The patient demographics are shown in Table 5. The average dose per day, average days of therapy, and frequency of the most commonly prescribed AC medications are shown in Table 6.

Table 4: Centrally Acting Drugs with AC Properties

TCA/ TCA Combinations	**Antispasmodics**
Amitriptyline	Atropine
Amitriptyline/chlordiazepoxide	Belladonna alkaloids
Amitriptyline/perphenazine	Belladonna L-alkaloids
Desipramine	Dicyclomine
Doxepin	Dicyclomine/phenobarbital
Imipramine	Hyoscyamine
Nortriptyline	Scopolamine
Antiparkinson Agents	**Urinary Antispasmodics**
Benztropine	Oxybutynin
Trihexyphenidyl	Tolterodine
Antipsychotics	**Antihistamines**
Chlorpromazine	Diphenhydramine
Clozapine	Hydroxyzine
Olanzapine	Promethazine
Promazine	
Thioridazine	

Table 5: Patient Demographics

Age (yrs), mean ±SD	75 ±7.3
Females	52.8%
Racial Distribution:	
White	69.7%
Black	14.6%
Hispanic	3.7%
Asian	1.6%
Other or unknown	10.4%
Severity Score:	
Baseline (no CCs)	23.3%
Moderate CCs	38.6%
Major CCs	27.8%
Catastrophic CCs	9.5%
Unknown	0.7%
Discharge to an institutional setting	20.6%
Documented delirium	1.2%
Median LOS (days)	4.0

Table 6: Most Commonly used AC Drugs in the Hospitalized Elderly

Drug	Frequency (%)	Average dose/day (mg)	Average days of therapy
Diphenhydramine	46	46.5	1.8
Promethazine	22.2	34	1.8
Atropine	9.1	1.6	1.1
Olanzapine	3.8	8.7	4.8
Oxybutynin	3.5	10.2	4.5

For the stepwise regression only 68,697 inpatients from the dataset were included. This was the total number of inpatients that were taking at least one AC drug and had a complete data set. The regression found that severity score, discharge status and whether or not the patient received an AC drug were the most statistically significant predictors of LOS with an r^2 of 0.29. The model accounts for 29% of the variability in the LOS. AC burden was determined to be statistically significant in relation to length of stay, with only the severity score and discharge status as more significant, respectively. The r^2 value was 0.326 and this demonstrated that the higher the AC burden for an elderly inpatient, the longer their hospital stays.

3.1.4 Discussion

AC medication administration is common in older adults especially in a hospitalized setting. Approximately one third of the inpatients without dementia in this study were on an AC medication. Previous studies have shown a link between the use of diphenhydramine, an AC medication, and an increase in length of hospital stay as a result of an adverse drug event

(Agostini et al, 2001). This study demonstrated the same result indicating that intervention should be evaluated to prevent this outcome.

AC burden is defined by Kay et al as the cumulative effect of taking multiple medications with AC activity (Kay et al, 2004). There are different ways to determine this burden, one method is developing an equation as was done in this study. The equation for AC burden was developed by using the Geriatric Dosage Handbook as a reference in assigning high, medium or low doses and in determining potency. This approach was used because this is a retrospective study and blood samples were not available to run a radio receptor assay. The equation method is an estimate as a true value cannot be determined because each individual's pharmacokinetics is different. Therefore, further studies are needed to validate the equation. Other limitations of the study include the observational and retrospective nature of the study design, which limits the ability to draw conclusions about causality in the association between AC drug use and hospital LOS. In addition, the data was collected from hospital data generated for reimbursement purposes and not for the specific purposes of this study. This limits the kind of information and the level of detail available for the study. Also, the potential to cause different AC side effects is different for each drug depending on blood brain barrier penetration and muscarinic receptor subtype affinity. Effects were assumed to be additive when they may be synergistic. Drugs with low potential for AC side effects were not evaluated, but these drugs may contribute to a cumulative AC effect. Furthermore, delirium appeared to be poorly documented in this dataset, making it difficult to evaluate as a contributor to hospital LOS.

3.2 Cognitive, Functional and Behavioral Outcomes Associated with Anticholinergic Drug Use in Alzheimer's Disease Patients Taking Cholinesterase Inhibitors

3.2.1 Background and Significance

Many different types of medications possess AC properties. These medications can be divided into two groups, those that are used therapeutically for their AC effects and those that do not derive their therapeutic benefit by blocking acetylcholine receptors, but have AC side effects. The first are used to treat clinical disorders frequently comorbid with AD including Parkinson's disease and urinary incontinence. Additionally, some may be prescribed to treat the side effects of cholinesterase inhibitor therapy (Hashimoto et al, 2000; Gill et al, 2005).

A number of studies have reported on the adverse effects associated with AC drugs in general elderly populations. A few studies have found elderly to be at risk of cognitive impairment even at low serum AC levels (Mulsant et al, 2003). Impairment of self-care capacity and cognition have also been found to be associated with high serum AC levels in dementia nursing home patients (Rovner et al , 1988). AD patients are at risk of additional impairment from AC drug therapy (Theinhaus et al, 1990). There is little data from clinical studies documenting the effects of concurrent AC and acetylcholinesterase inhibitor therapy on the cognition, function and behavior in AD patients. This group is expected to be at even greater risk for adverse effects of AC drugs due to age and disease-related changes. Surveys of administrative claims data from different state Medicaid plans have found that patients receiving cholinesterase inhibitors were also receiving AC drugs with significant central activity during a 3-month period (Slattum et al, 2001; Carnahan et al, 2006). In a retrospective study of 69 patients with AD taking donepezil, 16 received concurrent AC medications and experienced a significant decline in cognitive function over two years compared to patients with no concurrent AC medications (Lu et al, 2003). A follow-up to this study provides preliminary data that shows a non-significant decline in physical activities of daily living and instrumental activities of daily living (Bottiggi et al, 2006).

The hypothesis that guided this research was that the administration of AC drugs impairs memory, function, behavior and drug therapy efficacy in AD patients taking cholinesterase inhibitors. The specific aims for this project included assessing the changes in cognition, function, and behavior over time in AD patients taking cholinesterase inhibitors and drugs with AC properties. Additionally, to identify AC medication- and patient-related factors relevant to cognitive, functional, and behavioral outcomes in this population.

3.2.2 Methods Introduction

This study was modified several times in an attempt to address barriers of feasibility and recruitment. The original study was an intervention using three local physicians. The physicians were unable to participate for various reasons, and the study was changed to an observational design. The initial observational study required a blood draw in order to use SAA to quantify AC burden. The participants would still have had three visits, but they were required to have their visits at Medical College of Virginia (MCV) in order for the blood to be drawn. Participants were unwilling to come to the downtown academic medical center due to the traffic and nature of a hospital setting. This prompted a change to find another method of calculating burden without a blood draw to enable patients to be seen at a preferred location such as their home. The study was changed to use a scale, specifically the Anticholinergic Drug Scale, as a method of burden quantification. The main reason for the many changes to this study design was difficulty in patient recruitment.

3.2.2.1 Study Design

This observational study was conducted in participants with probable AD taking a ChEI in addition to either a low AC burden or a high AC burden. The total number of participants needed was 90 with 45 in each of the two AC groups. Selected participants underwent three assessments of cognition, function and behavior, three months apart in order to determine the rate of decline in outcome measures. These assessments were performed by a blinded student investigator and a graduate student. Demographic data including age, sex, residence, years of education, current diagnoses, duration of AC drug use, time since AD diagnosis, current AC dosing regimen, current dosing regimen of acetylcholinesterase inhibitor, indication for AC medication, other concurrent medications, and perceived effectiveness of AC and cholinesterase inhibitor medications were obtained on the Patient Intake Form (Appendix A). Furthermore, demographic data for the caregiver was collected using the Caregiver Intake Form (Appendix B). Quantification of AC activity resulting from the various AC medications taken by the participants was determined using the AC Drug Scale (ADS). An acetylcholinesterase equivalent dosing chart was used as a means of normalizing cholinesterase inhibitor exposure.

3.2.2.2 Participants

Participants were eligible for inclusion in the study if they had a diagnosis of probably AD based on medical history, mental status evaluation, clinical examination, or other tests as outlined in the Differential Diagnosis of AD Algorithm from the Alzheimer's Association (www.alz.org/Health/Diagnose/procedure.asp). Diagnosis was confirmed by the referring physician or the patient's primary care physician with authorization from the legally authorized representative. Participants were required to have a Mini-Mental State Examination score of 16 to 24, which corresponds to mild to moderate disease. In addition, participants had to be taking

a ChEI chronically. All of the currently available ChEIs were included, tacrine, donepezil, rivastigmine and galantamine. Chronic use of a medication was defined as daily use for greater than 30 days. Additionally, participants had to be medically stable without evidence of acute medical or psychiatric illness. Furthermore, they were excluded if they had problems with visual acuity, hearing or motor disturbances that were severe enough to prevent completion of testing procedures. Potential participants were also required to have a representative that was able to provide written informed consent to participate in the study. The participant themselves were required to provide assent to participate. In addition, a knowledgeable caregiver who was able to participate in the outcome measurements was required. A knowledgeable caregiver is defined as the primary person in charge of caring for an individual with Alzheimer's disease, usually a family member or a designated health care professional. If the potential participant was residing in a home or facility they were required to have a caregiver present. Selected participants were assessed at the location of their choice or at the VCU General Clinical Research Center.

Group 1 participants were taking at least one centrally-acting AC drug chronically. AC drugs were defined as one of the following: tricyclic antidepressants (amitriptyline, doxepin, imipramine, desipramine, nortriptyline), sedating antihistamines (diphenhydramine, hydroxyzine, promethazine), antiparkinson's drugs (benztropine, trihexyphenidyl, biperiden, procyclidine), urinary antispasmodics (oxybutynin, tolterodine, darifenacin, propantheline, solifenacin), gastrointestinal antispasmodics (atropine, scopolamine, hyoscyamine, belladonna alkaloids, dicyclomine), and antipsychotics (chlorpromazine, clozapine, promazine, thioridazine, olanzapine). Group 2 participants were taking no centrally acting AC drugs from the list above on a chronic basis.

Potential participants were recruited through physicians who treat Alzheimer's patients in the Greater Richmond area. Physicians were provided with the study protocol and advertisements. Advertisements were shared with prospective volunteers who contacted the PI if they were interested in screening for the study. Participants were also recruited through the Alzheimer's Association, Greater Richmond Chapter and the Commonwealth of Virginia Alzheimer's Commission. The Alzheimer's Association was provided with advertisements that could be included in the association newsletter, distributed at support groups and conferences, and other venues. Also, advertisements were placed in *Senior Living* magazine and other organizations in the senior network. The referring physicians, the Alzheimer's Association and other organizations did not provide names or contact information of potential participants directly to the PI.

The PI or co-investigator conducted the informed consent and assent processes with the participant and their representative. The participant and their representative received a copy of the consent form, reviewed it with the PI or co-investigator, and had an opportunity to discuss it with the PI or co-investigator. Consent was documented in writing.

3.2.2.3 Outcome Measures

Outcome measures were collected during three study visits three months apart with the participant and their knowledgeable caregiver. Assessments were made by the student investigator and a graduate student. Both were fully trained by an experienced psychologist (Dr. Ayn Welleford, Department of Gerontology, VCU) to administer all of the outcome assessments.

To avoid potential bias, each participant was de-identified using a number. Participants were offered a rest break between measurements.

3.2.2.3.1 Assessments

The specific outcome measures used in this study included the cognitive measures of Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) and the Mini-Mental State Examination (MMSE) with clock drawing. Functional outcomes included the Physical Self-Maintenance Scale (PSMS) and behavioral outcomes were assessed using the Neuropsychiatric Inventory (NPI). The last outcome measured was delirium using the Delirium Rating Scale-Revised-98.

The ADAS-Cog was the primary assessment of cognition. It is an 11-item test that measures the disturbances of memory, language, praxis, attention and other cognitive abilities which are often referred to as the core symptoms of AD with a score ranging from 0 to 70 with higher scores corresponding to more impairment. This test was used in the anti-dementia trials and is considered the gold-standard. Cross-sectional and longitudinal studies have shown that the total score on the ADAS-cog correlates with disease severity (Sevigny et al, 2010). Moreover, studies have shown that the ADAS-cog has high sensitivity and specificity for evaluating disease severity (Pera-Casanova, 1997).

The second cognitive assessment tool was the MMSE with clock drawing, which was performed to facilitate comparison of the results with other studies. This test is a simple and brief standard mental status exam routinely used to measure a person’s basic cognitive skills. This 11-item instrument evaluates several cognitive domains such as short-term memory, long-term memory,

orientation, registration, attention, visual construction skills and language. Scores range from 0 to 30, with higher scores corresponding to less impairment. The MMSE has sensitivity (87%) and specificity (82%) in the identification of dementia (Rosselli et al, 2006).

The PSMS, the functional instrument, is a brief assessment of the activities of daily living, specifically the ability to perform self-care, self-maintenance and physical activities. It is a six-item scale that rates self-care ability in toileting, feeding, dressing, personal hygiene and grooming, locomotion (physical ambulation), and bathing. It is based on the information provided by caregivers. For each activity, the patient is rated from 1 (independence) to 5 (dependence), hence higher scores are indicative of more impairment (Lawton et al, 1969).

Behavior was assessed using the NPI, a tool that evaluates 10 disturbances associated with dementia. These include delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, and aberrant motor activity. There are two additional behaviors that are assessed including night-time behavior disturbances, and appetite and eating abnormalities. The NPI measures both frequency and severity of each behavior. This assessment also uses caregiver input to assess these disturbances. A high score on this instrument is associated with greater impairment (Cummings et al, 1994).

The last assessment used in this study was the Delirium Rating Scale-Revised-98, a tool to evaluate delirium in the dementia participant. This is a validated, 16-item clinician-rated scale with 13 severity items and 3 diagnostic items, maximum total scale score of 46 points (includes the three diagnostic items) and a maximum severity score of 39 points (Trzepacz et al, 2001). It is not uncommon for older adults to suffer from drug-induced delirium with AC medications, especially in those with dementia (Gareri et al, 2007).

3.2.2.3.2 AC Burden Quantification

The ADS was used to calculate AC burden in the participant at each visit. This was done by obtaining a full list of medications from the participant. The ADS quantifies the AC potency of each medication based on ratings. Each medication, both chronic and as needed, was rated on a level of 0 to 3. Level 0 medications have no known AC properties; level 1 medications are potentially AC based on receptor binding studies; level 2 medications have been shown to cause AC adverse events at excessive doses; and level 3 medications are known to be markedly AC. A list of medications that are rated as 0 to 3 is provided in Appendix B (Carnahan et al, 2006). The ratings were then added together to determine the ADS total score. If a medication is used as both a scheduled and as needed medication then its rating is added twice.

3.2.2.3.3 ChEI Categorization

A ChEI dosing table was used to categorize the dose as initial, middle or maximal since the medications have been shown to have similar efficacy (Wilkinson et al, 2002; Liston et al 2004). The initial dose of donepezil is 5 mg and the maximal dose is 10 mg. The initial dose of rivastigmine is 3 mg, the middle dose is 6 mg to 9 mg and the maximal dose is 12 mg. The initial dose of the rivastigmine patch is 9 mg and the maximal is 18 mg. The initial dose of galantamine immediate release and extended release is 8 mg, the middle dose is 16 mg and the maximal dose is 24 mg.

3.2.2.4 Statistical Analysis

3.2.2.4.1 Sample Size

The calculation of the number of required participants for this study was based on a study conducted in non-demented and probable Alzheimer's patients where SAA was correlated with cognitive performance with r = 0.29 (Theinhaus et al, 1990). The sample size necessary to detect a similar correlation in our study ($\alpha = 0.05$, $\beta = 0.20$, for a one-sided test) is 67. A second basis for the sample size was a t-test comparison of low and high AC burden patients. It was assumed that patients with mild to moderate AD with high AC burden will behave as patients receiving a placebo rather than a ChEI. Data on change from baseline in ADAS-cog score for placebo treated and optimally treated patients can be used to estimate sample size. In a study of patients with mild to moderated AD, the weighted mean difference in change in ADAS-cog score over six months for placebo and donepezil treated patients was 2.92 with equal SD of 5.5 (Birks J, 2006). The sample size necessary to detect a similar difference ($\alpha = 0.05$, $\beta = 0.20$, for a one-sided test) is 45 per group.

3.2.2.4.2 Analysis Plan

The change over 6 months for each clinical outcome was to be compared for Groups 1 and 2 using a one-sided t-test ($\alpha = 0.05$). If assumptions of the t-test were not met, data transformation and alternative approaches would be explored. This analysis assumes that participants would remain in the high or low burden group throughout the six month study period. After the first 20 participants completed the study, the validity of this assumption was to be assessed. Based on the results of the first 20 participants, the study analysis plan might have been adjusted. Additionally, in the case that an alternative plan was needed the data collected at the 3-month assessment could have been used in the analysis.

The relationship between each clinical outcome and anticholinergic activity at each visit was to be evaluated using multiple regression. Demographic variables (patient and therapy-related factors) and cholinesterase inhibitor dose category would be included as dependent variables in each analysis. Statistical analyses were to be performed using SPSS Version 16.0 for Windows.

3.2.3 Results

The study was closed in the Spring of 2010 due to low enrollment. During the two years that the study was open there were three participants that completed all three study visits. There were two more participants who were unable to maintain the minimum MMSE requirement at the first visit. Subject 4 was unable to finish the assessments due to aggression and agitation. It was determined that she would be unable to continue the study due to the progression of her disease. Subject 5 was cooperative, but had a MMSE score of 12/30 following the first meeting. This fell below the 16/30 minimum requirement.

Of the three participants that completed the study, one had high AC burden and the other two fell into the low AC burden group. The demographics are shown in Table 7. For all three participants there was no change in the AC medications or in the ChEIs and NMDA receptor antagonists that they were taking over the six month time period. All three participants were taking donepezil and two of the three were taking memantine. The average age of the participants was 71.7 ± 12.0. As shown in Appendix A, there were several domains collected on each participant, but the questionnaire was incomplete for some of the participants. Hence only the variables listed in Table 7 were complete for all participants.

Table 7: Demographics

	Subject 1	Subject 2	Subject 3
Age	84	71	60
Sex	Female	Male	Male
Marital Status	Married	Married*	Married
Ethnicity	White	Black	White
Residence	ALF	Home	Home
Education	16	12	20
Smoking	No	No	No

* Widowed after 2nd visit

The summary of the outcomes for each participant is located in Table 8. As shown in Table 8, Participant 1 has the highest ADS score that corresponds to the lowest MMSE and ADAS-cog scores. Participant 1 was taking solifenacin which is known to be markedly AC based on SAA studies. The NPI scores did not conform to the trend that was seen between ADS scores and cognition as well as function. Regression analyses were not performed due to the small sample size.

Table 8: Summary of Outcome Measures

	Visit 1			Visit 2			Visit 3			Average ± Std Dev		
	Subject 1	Subject 2	Subject 3	Subject 1	Subject 2	Subject 3	Subject 1	Subject 2	Subject 3	Subject 1	Subject 2	Subject 3
ADAS-cog	29.0	18.0	25.0	26.0	16.0	26.0	41.0	20.0	30.0	32.0 ± 7.93	18.0 ± 2.00	27.0 ± 2.65
MMSE	17.0	24.0	20.0	19.0	24.0	20.0	17.0	24.0	21.0	17.7 ± 1.15	24.0	20.3 ± 0.58
Delirium	13.0	6.0	9.0	15.0	7.0	11.0	14.0	5.0	13.0	14.0 ± 1.00	6.0 ± 1.00	11.0 ± 2.00
NPI	3.0	11.0	38.0	3.0	10.0	29.0	3.0	0.0	28.0	3.0	7.0 ± 6.08	31.7 ± 5.51
Caregiver Occupational Distress (NPI)	2.0	9.0	14.0	2.0	5.0	13.0	2.0	0.0	8.0	2.0	4.7 ± 4.51	11.7 ± 3.21
PSMS	11.0	9.0	6.0	13.0	9.0	8.0	13.0	6.0	8.0	12.3 ± 1.15	8.0 ± 1.73	7.3 ± 1.15
ADS	3.0	0.0	0.0	3.0	0.0	0.0	3.0	0.0	0.0	3.0	0.0	0.0
ChE	Maximal	Initial	Maximal	Maximal	Initial	Maximal	Maximal	Initial	Maximal	Maximal	Initial	Maximal

3.2.4 Discussion

The lack of participants accounted for the premature termination of the study. Much time was spent on advertising to caregivers and healthcare workers to no avail. The three participants were recruited by means of different avenues. Participant 1's caregiver contacted the PI about the study, while Participant 2 was recruited by their physician and Participant 3 by the local Alzheimer's Association chapter. There were barriers that were faced in recruitment of participants. Many of the barriers were legal in nature with the nursing homes, assisted living facilities, and adult day centers. These facilities required approval from the power of attorneys (POAs) or family members in order for the patients or residents participate. In addition, many of these facilities were not willing to send a letter with the advertisement to the families and POAs. For the few adult day centers interested in participating, there was either a lack of interest among the families/POAs or the patient did not meet the requirements to participate. One assisted living facility that also had an independent living section, allowed for the advertisement to be posted in the pharmacy. This was the advertisement that Participant 1's husband saw. As discussed previously, spousal and family support was a significant barrier to participating in research studies. The study by Marcantonio et al. in 2008 found that approximately 55% of potential participants indicated that they would decline if their spouse was not interested or did not approve of the research (Marcantonio et al, 2008).

Another barrier that was faced was associated with physician support. Physicians from the Alzheimer's Association referral list of doctors who treat AD patients were contacted and asked to facilitate patient recruitment. Many physicians chose not to participate in either providing a flyer to the possible participant or posting the flyer in their office or practice site. This may be

due to the perceived additional work that is involved in assisting to recruit patients. Additional barriers may have been bias towards research or lack of belief in the importance of the research question (Sullivan-Bolyai et al, 2007).

One additional barrier may have been perceived benefit. AD is an irreversible disease that leads to significant loss of quality of life. This study was not a treatment study and therefore may have been considered a less worthwhile project to participate in.

There was a great deal of variability between the three participants that may have contributed to their cognitive, behavioral and functional scores. Participant 1's caregiver was her husband yet did not live with her in her apartment unlike the other two. Furthermore, she had a twin who had passed away from AD. Participant 2's third visit NPI and PSMS scores were based on information provided by the daughter who did not live with him. His wife had passed away not long before the third visit. This is likely why the *NPI* and the *Caregiver Occupational Distress* scores were significantly less than the previous visits. Participant 3's caregiver was the only one who worked outside the home and had younger children. This explains in part the significantly higher *NPI* and *Caregiver Occupational Distress* scores. These factors make any generalizations impossible as does the small sample size.

The student investigator was present at all visits and performed all cognitive and delirium assessments. The additional graduate student was present at all 3 of Participant 1 and 2's visits. Also, she completed the PSMS and NPI with the caregivers for these two subjects. Therefore, inter-rater reliability was high.

In conclusion, this study had the potential to provide valuable evidence as to whether AC burden has a negative effect on cognition, function, and behavior in AD patients. Due to the multiple barriers associated with recruiting participants this study was terminated. Further research in this area is necessary as the pharmacological potential for negative consequences of AC burden in AD may not translate to clinical adverse events. Moreover, further research is needed in overcoming barriers associated with AD patient and caregiver participation. This will provide for greater participation in important studies that may improve the quality of life patients and their caregivers.

3.3 Chapter Summary

This chapter described two preliminary research studies. The first is still ongoing, but the initial findings support other research with respect to the prevalence of 33% and the increased LOS associated with use of AC medications. As shown in Table 2 from Chapter 1, within the last 30 years the prevalence has ranged from as low as 6% to as high as 80%. The majority of the studies found that the range was about 20%-30%. Additionally, the study by Agostini et al, found that length of stay was increased with the use of diphenhydramine. The results from the second study are inconclusive with so few participants. With growing evidence for the high prevalence of AC medications and the negative effects associated with their use in older adults, it is imperative that more research be conducted in dementia patients using these medications. The second study had the potential to evaluate the use of AC medications on dementia patients, but due to recruitment barriers, this was not completed. The next option is to perform a retrospective analysis of dementia patients, which is the basis for the study discussed in the next chapters.

Chapter 4

Methods

4.0 Chapter Introduction

This chapter describes the methods for a retrospective, longitudinal study that was conducted using data from patient charts for dementia patients receiving care at Piedmont Geriatric Hospital. This study was derived from the prospective preliminary study discussed in the previous chapter. Hence the same outcomes of function, behavior and cognition were evaluated, but through different assessments. Additionally, the objective of evaluating the association between AC burden and functional, behavioral and cognitive outcomes was the same as the preliminary study. The patients were identified by the hospital and then charts were reviewed to obtain the demographic, pharmacy and outcome information. This data was compiled and then statistical analysis was preformed to identify any associations between the outcomes and AC burden. The process is described in detail below.

4.1 Effect of Anticholinergic Burden on Functional Outcomes in Patients with Dementia

4.1.1 Study Design

The study was a retrospective observational study of moderate to severe dementia patients at a state geriatric facility. Both the VCU Institutional Review Board (IRB) and Piedmont Geriatric Hospital (PGH) IRB approved the study protocol.

PGH is Virginia's only state facility exclusively for older adults aged 65 and over with mental illness. It is a 135-bed hospital located in rural Burkeville, VA. Typically only about 122 to 128 beds are filled at any given time. The patient length of stay varies from a few days to several years depending on the severity of the patient's condition (Piedmont Geriatric Hospital, 2010). The hospital requires that authorization be received to use any chart information, including non-personal health information (PHI). A letter was used as informed consent and sent out to the family and representatives for the patients' who were still living. This letter is included in Appendix C. The families and representatives were given two weeks to decline interest. A non-response was deemed as an agreement to be included in the study.

Charts dated from 2000 to the present were reviewed to obtain the monthly nursing reports. Data from the reports were recorded for the first six months and the last six months of the hospital stay for every individual. Data from the in-between months were collected quarterly. As an example, subject "A" was a patient at PGH from January 2002 through December 2003, therefore January 2002 to June 2002 was recorded monthly, followed by September 2002, December 2003, March 2003 and then monthly from July 2003 to December 2003. Therefore a total of 15 time points were recorded for subject "A." When a patient is admitted to PGH it is because they present a danger to themselves or others, require continuous care, or have needs that cannot be met properly by a nursing facility or assisted living facility (Piedmont Geriatric Hospital, 2010). Hence they usually require stabilization upon admission and this is typically accomplished by changes in the medication regimen. Therefore the first six months were collected in order to account for any changes that the alteration in medications may have on their function, behavior and cognition. The last six months were collected to measure the changes in progression at the

end of the disease for those that had deceased at PGH and the progression to stabilization for those that were discharged.

In addition to the nursing report, demographic information was collected from the physician, social worker and psychologist notes. The prescription history for every month that the patient's nursing report was recorded was noted. The IRB approved collection form is included in Appendix 4. This form does not include any PHI and therefore this study was approved as an exempt IRB protocol.

4.1.2 Participants

Patients were selected if they had a diagnosis of dementia and had been at PGH within the last six years. Six years was chosen because the pharmacy only keeps records for six years. These patients were identified by the health information management (HIM) specialist, Peggy Vaughn, who worked with the billing department to identify potential subjects. There were 56 patients that were deceased at the time of the identification and then additional 37 patients who had to be contacted as they were alive and no longer at PGH. These 37 patients had a letter sent to their family/representative. There were 10 patients whose family or representative declined their participation or the letter did not reach them. Therefore there were a total of 83 patients included in this study.

Initially only patients with a diagnosis of AD were to be included. After the billing records were checked there were only 28 patients with a primary diagnosis of dementia. The computer billing program is unable to identify patients by their secondary diagnosis. Therefore if a patient's primary diagnosis is Parkinson's disease with a secondary diagnosis of AD or dementia, then

they will not be added to the report. Based on this information the diagnosis of interest was widened to all dementia to increase the number of potential participants in the study.

Another method of increasing participants in the study that was attempted was to use records from the other state facilities that had geriatric patients with dementia. The issue that arose was the measures of function, cognition and behavior varied across all of the facilities and there was not a clear method of standardizing the assessments between hospitals. While PGH used the Functional Independence Measure Scale (FIMS), another facility, Catawba Hospital relied upon nursing notes rather than a specific assessment tool for the measurement of function. Therefore all of the participants in this study were from PGH.

4.1.3 Data Collection

The student investigator (S. Dharia) went to PGH on several occasions to obtain the data. The sources of patient information were the medical chart and the pharmacy database, if needed, for prescription history. In terms of prescription history, any prescriptions prior to 2004 had to be collected from the chart only. Much of the pharmacy medication record was already in the chart. The charts used were located in the medical records room, on microfiche, in the overflow chart room, or on the units. For patients who were deceased or discharged the first two locations were where the majority of information was collected. The second two locations were for patients that were still at PGH or that were just recently discharged. The list of patients identified by HIM was used to find the charts. As mentioned above, the majority of information was collected from the healthcare notes. The nursing report was located in the middle section of the chart along with the daily medical notes. The pharmacy monthly prescription information was found at the beginning of the chart. The physician, social worker and psychologist notes were all found in the

first chart that the patient had. The majority of the patients had more than one chart as only six months was allocated to each one. The records from 2000 to 2010 were reviewed for patient and disease specific information. Data prior to this date was not collected as the specific outcome assessments were not in use prior to 2000.

Many of the patients had multiple admissions during the course of their disease progression, therefore only their first admission was included. This was done to ensure that the rate of progression was captured with as few external influences and to limit variability on the patients' progression through the disease. Additionally, as indicated above when a patient is admitted to PGH, stabilization of the patient's condition is required and therefore each admission would alter the rate of progression of the disease.

As mentioned above in the study design section, data from the first six months and last six months, if available, were collected for each patient's stay. Additionally, for the months in between, data was collected quarterly.

The specific data collected included age, sex, marital status, ethnicity, length of stay, number of admissions, residence prior to admission, education, smoking and alcohol use status, conditions at first admission, year of dementia diagnosis, and ChEIs and memantine use. The ChEIs and memantine use was collected from the charts, under the pharmacy prescriptions and the physician notes from admission that documented past medication history. This data was collected as past research has shown that these factors may influence the progression or the improvement of dementia (Alzheimer's Association 2010)(Birks J, 2006). As mentioned above, PHI including name, date of birth, admission and discharge dates were not recorded to protect patient privacy. This specific information was needed to identify the patient charts, collect the

data and match the pharmacy data from the chart with the pharmacy database. The student investigator (S. Dharia) and on one occasion for one patient a gerontology student recorded the information. These two students underwent required HIPPA training prior to collecting or recording any information.

The coding scheme for the variables is located in Table 9. All other variables remained continuous.

Table 9: Variable Coding Scheme

Variable	Coding Scheme
Sex	"male" = 0; "female" = 1
Marital Status	"married" = 1 "single" = 2 "widowed" = 3 "divorced" = 4 "separated" = 5 "unknown" = 9
Ethnicity/Race	"White" = 1 "Black" = 2 "Hispanic" = 3 "Asian/Pacific Islander" = 4 "Native American" = 5 "unknown" = 9
Residence Prior to Admission	"home with no assistance" = 1 "home with assistance" = 2 "assisted living facility" = 3 "skilled nursing facility" = 4 "unknown" = 9
Education	"<K-5" = 1 "K-5" = 2 "6-8" = 3 "9-12" = 4 ">12+" = 5 "unknown" = 9
Smoking	"no" = 0 "yes" = 1 "unknown" = 9
Alcohol	"no" = 0 "yes" = 1

Variable	Coding Scheme
	"unknown" = 9
AD Medications	"donepezil" = 1 "rivastigmine" = 2 "galantamine" = 3 "memantine" = 4 "unknown" = 9
Conditions Present on Admission	"yes" = 1 "no" = 0 "unknown" = 9
Change in Cognition	"change" = 1 "no change" = 2
Change in Behavior	"change" = 1 "no change" = 2

As mentioned above, monthly medication lists were collected from the chart and the pharmacy dispensing database. The pharmacy dispensing database was only searched when the information was not available in the chart. If there was a disagreement between the two sources of prescription information, the physician notes and the nurses' medication log were checked and verified. Specifically, all medications and their dosages for each patient were collected. The medication information was collected for every month that was recorded. As a clarification, drugs for the first six months, last six months and then quarterly in between were collected. This information was used to determine the AC burden score using the ADS (Carnahan et al, 2006).

The ADS, as mentioned in the introduction, is a non-invasive method of AC burden quantification. This method assigns ratings of 0 to 3 for a list of medications. This list is in Appendix B. The ratings are defined as follows, level 0 = no known AC properties; level 1 = potentially AC as evidenced by receptor binding studies; level 2 = AC adverse events sometimes noted, usually at excessive doses; and level 3 = markedly AC. The ratings were then added together to determine the ADS total score. If a medication was used as both a scheduled and as

needed medication then its rating was added twice. For instance, if a patient was taking tolterodine (ADS = 3) for urinary incontinence, alprazolam (ADS = 1) for anxiety as needed and alendronate (ADS = 0) for osteoporosis, the total ADS score for this patient would be a 4. This method was chosen for its use in a retrospective study using medical records. The DBI would have been another option, but it only considers dose and not the level of AC activity as the ADS does. The ideal scale would have taken both into consideration.

4.1.4 Assessments

The clinical outcome of interest for the primary study objective was the change in function over time. This objective was to assess the function in dementia patients with varying AC burden. To accomplish this, functional information was collected from the chart, specifically from the Functional Independence Measure Scale (FIMS) that is part of the monthly nursing report. This scale was originally developed to assess functional gains in patients undergoing rehabilitation for a stroke. Since then it has become widely used in rehabilitation facilities and for the measurement of activities of daily living (ADLs) in dementia patients (Cotter et al, 2002). The FIMS is also used at Veterans Administration hospitals and in continuing care centers. This measurement assesses how independent a person is on a scale of 1 to 7. Where 1 = complete dependence and 7 = complete independence. The original scale assesses the areas of self-care (grooming, dressing, eating, etc.), sphincter control, mobility, locomotion, communication and social cognition (Oczkowski et al, 1993; Amundson et al, 2010). As a measure for ADLs in dementia patients the scale was modified to all areas but the communication and social cognition portions (Cotter et al, 2002). A study by Cotter et al showed that this tool is as effective in measuring ADLs as caregiver reports (Cotter et al, 2002). This tool would decrease the amount

of time spent writing a monthly note about the patient's ADL status, which was method of assessment prior to 2000 at PGH. In addition, this is a standardized method of assessing function when there are several nurses involved in the patients' care. As mentioned above the FIMS was first used in 2000 and then through the years it was further modified. The original modified scale used at PGH in 2000 measured 13 areas including eating, grooming, bathing, dressing upper, dressing lower, toileting, bladder management, bowel management, bed to chair or wheelchair transfer, ability to transfer to toilet, tub/shower, walking or use of wheelchair, and the ability to use the stairs. The newer modified version that PGH started using in 2007 only had 9 items and did not include the transfer from bed to chair/wheelchair, transfer to the toilet, tub/shower transfer or use of stairs. It not known why a modified version was used or why it was further shortened in 2007. It may have been that communication and social cognition are impaired in the majority of patients who are admitted to PGH. Additionally, patients never take the stairs at PGH and many of the patients are in wheelchairs or require assistance to the toilet or shower. As the FIMS is part of the nursing report, the nursing staff fills it out. The extent of the training given to the nurses on the FIMS is unknown.

The secondary objectives were to assess the cognition and behavior in dementia patients with varying AC burdens. Cognitive status and behavioral status were evaluated using the Monthly Nursing Recovery Summary attached to the FIMS score. The notes provided nursing observations of behavior and cognition collected for each particular month. The first page of the nursing report was dedicated for the documentation of behavior and cognition. These notes were then interpreted only by the student investigator (S. Dharia) as a change or no change from the previous month or report. Change referred to worsening behavior or cognition. In many reports, there were notes of "increased hitting" or "more confusion," which were then both coded as a

change. In other reports, the notes would say "1 instance of hitting" and then the next month would say the same thing. This was translated as no change from the month before. A positive change was rare, but if it did occur it was minor and categorized as no change. If the positive change was significant then a notation would have been made on the collection form that behavior or cognition had improved from the month or quarter before. There were no instances of significant positive change for any of the patients.

4.1.5 Statistical Analysis

Descriptive statistics were used to describe the data. Also, regression analysis was used to explore the relationship between the outcomes and ADS scores. Data from the collection forms was complied into an Excel spreadsheet. Excel 2007 and SPSS 18.0 were used to calculate descriptive statistics including mean (median and range), percentages and total counts.

Additionally, the FIMS scores were plotted to assess the distribution and assess for normality. The distribution was found to be a more s-shaped distribution. Data transformations were performed to obtain a normal distribution. The distributions were evaluated using the Shapiro-Wilk test, the Q-Q plots, the histograms, and the box-plots. The distribution was kept at normal and the link function as identity. These are the pre-set model types for linear scale responses. For the cognitive and behavioral outcomes the model type was selected as binary logistic. This was because the data was "yes/no" responses to change.

A sample size calculation was performed using the following equation:

$$n = 2\sigma^2 \left(z_\alpha + z_\beta\right)^2 (1-\rho) \div \delta^2 m$$

Where z_α is the z-score for the alpha level, which is 0.05 for a two-tailed test, and therefore 0.025 for this situation. The z_β is the z-score for the beta level or Type 2 error and 0.80 for 80% power. The σ is the estimate of the standard deviation which is equivalent to the FIMS minimum score subtracted from the maximum score divided by six. The ρ is the within-subject variance which is estimated to be zero in ideal cases. δ^2 refers to the minimum clinically important effect size. The literature was searched to find this value, two articles relating to dementia with the recorded effect sizes were identified. They were both for cognitive outcomes in dementia and not functional outcomes (Colcombe et al, 2003; Oken et al, 1998). Both articles found effect sizes to be an average of 0.45. This value was used in this equation. The *m* is the number of repeated of measures which in this case was the average of the number of observations for the patients. Using this equation it was determined that to see a difference a sample size of 435.47 or 436 patients was needed. Typically sample size calculations are used in experimental studies and not retrospective, observational ones. In this study, the sample size was much smaller than 436 participants and as mentioned in section 4.1.2 reaching this number was not achievable.

The relationship between outcomes of interest and the other variables were modeled using a generalized estimating equation approach (GEE). GEE was chosen over other statistical methods such as random effects as it makes fewer assumptions and therefore has a lower risk of bias. It is consistent even if the correlation structure is misspecified (Twisk, 2003). Also it is an appropriate method to use when the data is longitudinal in nature as in this study.

The data was reviewed and the participants with only one time point were removed as a change in function, cognition and behavior over time were the objectives of interest. Following this, a

correlation structure was selected based on a within subject correlation structure table. This table is based on the first six month time points and is displayed below as Table 10.

Table 10: Within Subject Correlation Structure

	Y1	Y2	Y3	Y4	Y5	Y6
Y1	-	0.014	0.121	0.165	0.207	0.253
Y2		-	0.109	0.138	0.179	0.226
Y3			-	0.027	0.067	0.115
Y4				-	0.042	0.091
Y5					-	0.048
Y6						-

There are five correlation structures that could have been selected including independent, exchangeable, m-dependent, autoregressive and unstructured. The independent structure was excluded as the correlations between measurements cannot be assumed to be zero. Furthermore, unstructured, which assumes that all of the correlations are different, was excluded due to computational challenges associated with a small sample size resulting in the estimation algorithm failing to converge. The autoregressive structure was initially eliminated as it works best with equally spaced time points. For this analysis, time was collected quarterly with each of the first six months and last six months collected as well. The data was then changed to accommodate this equally spaced requirement by using the first and the fourth month to run the analysis. Exchangeable assumes that the correlations between measurements are equal (Twisk, 2003). For this data that is not the case, but it may be an appropriate structure to use. M-dependent assumes that correlations one measurement apart are equal, two measurements apart are equal and so forth. This is a more appropriate structure, but it is less desirable for the data as

it is a relatively small set and m-dependent requires estimating additional parameters (Twisk, 2003).

The data was analyzed using these three specific structures, autoregressive, exchangeable, and m-dependent, for comparison purposes. The dataset minus those with only one time point was used to compare the exchangeable and the m-dependent structures only.

Additionally, a second modified dataset was created based on the patients who were at PGH for a minimum of six months. This second dataset was used as the correlation structure was based on these results. Exchangeable and m-dependent structures were used on this dataset.

A third dataset was created to run an autoregressive correlation structure. The months in this dataset were quarterly. Therefore for the first six months, months 2, 3, 5, and 6 were removed and then the same was done for the last six months.

Another analysis was run using the significant variables from the first analysis for all of the correlation structures and their corresponding data sets. Additionally, the insignificant variables that may have influenced them were included. The insignificant variables that may have caused a change of 20% or more in the coefficients of the significant variables were the ones that were included in this second analysis. This assesses for potential confounding in the variables. If insignificant variables cause a 20% or greater change in the estimates then it is said to be a potential confounder.

There were a total of 10 outputs for the different models listed above. The use of three correlation structures was only used for the assessment of the functional outcome. The cognitive and behavioral outcomes were evaluated using GEE regression for categorical data and used the

exchangeable structure as they are coded yes/no responses. There are a total of four outputs for both of these outcomes.

A goodness of fit test (QIC) was performed using SPSS and was used to evaluate how well the model fits the observations. This was then useful in determining which of the correlation structures was more appropriate. A Huber-White sandwich estimator was used as a way to ensure that the variances were robust. Specifically, robust variances are important as they provide accurate assessments of the sample-to-sample variability of the parameter estimates even if the model is misspecified (Norusis, 2008).

For the test of model effects, Type III, was selected for all analysis as it does not depend on the entry order of the variables like Type I does. Test Type III is typically preferred unless order of the variables is important, which in this case it is not.

There were several independent variables evaluated for the three outcomes including age, sex, marital status, ethnicity, length of stay, number of admissions, residence prior to admission, education, smoking and alcohol use status, year of dementia diagnosis, functional comorbidity index, constipation, and ChEI and memantine use.

The functional comorbidity index (FCI) is a tool that predicts function for patients who have comorbid diseases such as diabetes or COPD. The FCI was more effective in evaluating an association to physical function compared with the Charlson Comorbidity and the Kaplan-Ferinstein indices (Groll et al, 2005). It includes most common diagnosis, but as it is based on secondary data, there may be others that should have been included. Overall the FCI is a useful

tool and the only general population-based functional index. This tool assigns "1" if a person has one of the 18 diseases and "0" if they do not (Groll et al, 2005).

There was one select condition that may be considered a side effect of the use of AC medications that was included in this analysis, constipation. The other disease states recorded were not included in the analysis as only those in the FCI have been shown to have an association with functional outcomes. These conditions were still included in the descriptive statistics.

The α-level was set at 0.05. Statistical analyses were performed using SPSS Version 18.0 for Windows.

Chapter 5

Results

5.1 Results

5.1.1 Descriptive Results

There were a total of 83 subjects included in this study with a median age of 77 years and a range of 65 to 94 years at admission. Table 11 displays the demographics of the patients. The majority of the subjects were either married or widowed white males that were living in a nursing home or hospital prior to being admitted to PGH. Furthermore, the majority graduated high school or had some college. The participants were at PGH for a median of 536 days, with a range of 13 to 2973 days.

While all of the patients had a diagnosis of dementia, only 33.7% were taking a cognitive-enhancing medication. Of those 36 patients taking (or did so previously) a ChEI or memantine, the majority were taking donepezil as their first or second cognitive-enhancing medication. There were eight participants taking two cognitive-enhancing treatments during their stay a PGH. None of the patients took galantamine as their second medication. The median ADS score was 3.0 with the majority of patients having ADS scores ranging from 1 to 3. There were several AC medications that this sample received, divalproex, olanzapine, lorazepam, sertraline, and furosemide were the most commonly used.

Table 11: Demographics

Age (Years) at Admission	**Mean ± SD**
Average	78 ± 6
Sex	**% (N)**
Female	32.5% (27)
Male	67.5% (56)
Race/ Ethnicity	**% (N)**
White	63.9% (53)
Black	32.5% (27)
Hispanic	1.2% (1)
Asian/Pacific Islander	1.2% (1)
American Indian	1.2% (1)
Marital Status	**% (N)**
Married	34.9% (29)
Single	8.4% (7)
Widowed	31.3% (26)
Divorced	20.5% (17)
Separated	1.2% (1)
Unknown	3.6% (3)
Highest Education Achieved (Years)	**% (N)**
<K-5	10.8% (9)

K-5	2.4% (2)
6-8	21.7% (18)
9-12	36.1% (30)
>12+	24.1% (20)
Unknown	4.8% (4)
Residence Prior to Admission	**% (N)**
Home w/ no Assistance	15.7% (13)
Home w/ Assistance	19.3% (16)
ALF	8.4% (7)
SNF	55.4% (46)
Unknown	1.2% (1)
LOS	
Range (days)*	13-2973
Mean (days)*	769 ± 756
Median (days)*	536
Mean (months)^	19.6 ± 20.1

* number of days patient was in hospital during 1st admission
^ number of months from first FIMS (no earlier than 2000) to last FIMS score

As shown in Table 12, the FIMS score had a wide range with a median of 14. None of the patients had a maximal FIMS score of 81, the highest was 65. Due to this wide range of FIMS score, a test of normality was performed. The Q-Q plot for the non-transformed data is located in Figure 1. The Shapiro-Wilks test was used to assess for normality and it was significant with a p-value <0.01 indicating that the data were not normally distributed. Several methods were used to transform the data to obtain normality. None of the methods produced a non-significant Shapiro-Wilk's test. The Q-Q plots were assessed and the natural logarithmic transformation of the data produced a normal distribution visually compared to the other transformations (Figure 2). Additionally, the histogram and box-plots were assessed to determine the most appropriate data transformation. The plots and the histogram using the logarithmic transformation were much more normal visually than the other transformations and the original scores. Normality is not an assumption of GEE and research using GEE has shown to produce robust results with skewed data (Lee et al, 2007). Therefore the logarithmic distribution was used in the analysis.

Table 12: AD Treatment and Outcomes

AD Treatment	**% (N)**
Yes	33.7% (28)
Previous	9.6% (8)
First AD Medication*	**% (N)**
donepezil	50.0% (18)
rivastigmine	13.9% (5)
galantamine	11.1% (4)
memantine	25% (9)
Second AD Medication**	**% (N)**
donepezil	62.5% (5)
rivastigmine	25.0% (2)
memantine	12.5% (1)
ADS	
Range	0.0-11

Mean ± Std Dev	3.0 ± 2.1
FIMS Score	
Range	8.0 - 65.0
Mean ± Std Dev	19.1 ± 13.0
Change in Cognition^	**% (N)**
Yes	40.9% (464)
Change in Behavior^	**% (N)**
Yes	69.3% (786)

* Total n = 36
** Total n = 8
^ Total n = 1135, the number of total observations

Figure 1: Distribution of FIMS Scores

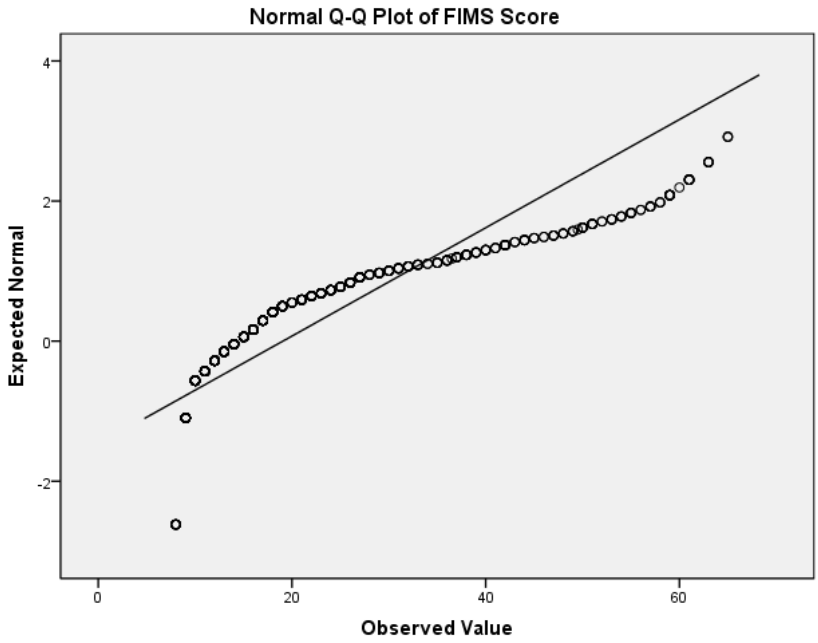

Figure 2: Distribution of the Natural Log of the FIMS Scores

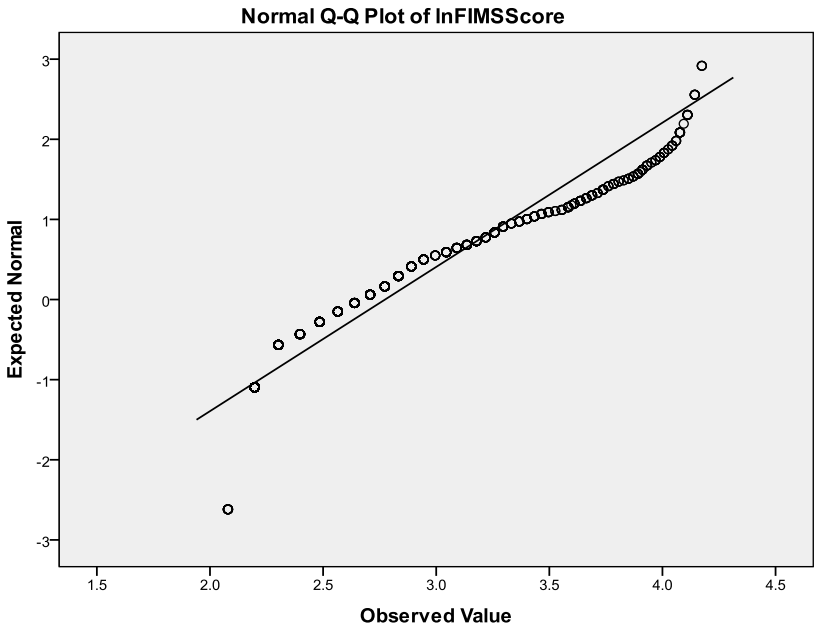

Table 13 displays the health related demographics. The majority of patients were non-smokers and about half either drank or were previous drinkers. There were some patients that had developed dementia due to heavy alcohol use. The most common disease conditions at admission were hypertension and other cardiovascular disorders, such as myocardial infarction (MI), stroke, congestive heart failure (CHF), coronary artery disease (CAD), and peripheral vascular disease (PVD). There were some conditions listed on the collection form that were not present in this patient population including certain gastrointestinal (GI) conditions such as diarrhea and nausea/vomiting. The average FCI was 2.2 with a range of 0 to 22. The FCI accounted for several disease states including, arthritis, osteoporosis, asthma, chronic obstructive pulmonary disease (COPD), angina, CHF, MI, Parkinson's disease (PD), stroke, PVD, diabetes, upper gastrointestinal diseases, depression, anxiety, visual impairment, hearing impairment, degenerative disc disease including osteoporosis, and obesity.

Table 13: Health Related Demographics

Smoking	**% (N)**
No	61.4% (51)
Previous	27.7% (23)
Unknown	4.8% (4)
Alcohol	**% (N)**
No	47% (39)
Previous	42.2% (35)
Unknown	3.6% (3)
Disease States on Admission	**% (N)**
HTN	63.9% (53)
Other CV	53.0% (44)
Constipation	44.6% (37)
High Cholesterol	27.7% (23)
Diabetes	26.5% (22)
Thyroid Conditions	22.9% (19)
COPD	22.9% (19)
Seizures	19.3% (16)
TBI	13.3% (11)
Urinary Incontinence	10.8% (9)
Arrhythmias	8.4% (7)
Depression	7.2% (6)
Delirium/Confusion	7.2% (6)
Cancer	6.0% (5)
Loss of Coordination	6.0% (5)
PD	6.0% (5)
Agitation	6.0% (5)
Asthma	3.6% (3)
Loss of Appetite	2.4% (2)
Bradycardia	2.4% (2)
Eyeglasses	2.4% (2)
Hearing Aids	1.2% (1)
Abdominal Cramps	1.2% (1)
Tachycardia	1.2% (1)
Pneumonia	0% (0)
Vomiting	0% (0)
Nausea	0% (0)
Diarrhea	0% (0)
Dry Mouth	0% (0)
Clots	0% (0)

5.1.2 Functional Outcomes

The use of the FCI enabled important variables to remain in the dataset, including the use of visual or hearing aids. Otherwise these would have been removed due to less than five values per disease state. Additionally, the patients who were only at PGH for a month or less were excluded. Therefore a total of 79 patients were included in the final analyses. There were a total of 1131 time points included for all 79 patients and none of the patients or time points were excluded. The minimum number of months was 2 and the maximum number of months for an individual was 40. Table 14 provides a description of the patients that were removed and why.

Table 14: Patients Excluded from the Analysis

Patient Number	Dataset Removed From	Reason for Removal (1 Time Point = 1 Month)
5	79 Patients / AR	< 2 time points
6	66 Patients / AR	< 6 time points
15	66 Patients / AR	< 6 time points
16	79 Patients / AR	< 2 time points
17	66 Patients / AR	< 6 time points
31	66 Patients / AR	< 6 time points
36	66 Patients	< 6 time points
37	79 Patients / AR	< 2 time points
38	66 Patients / AR	< 6 time points
39	79 Patients / AR	< 2 time points
40	66 Patients / AR	< 6 time points
41	66 Patients	< 6 time points
56	N/A	Patient record not found at PGH
63	66 Patients / AR	< 6 time points
64	66 Patients	< 6 time points
65	66 Patients / AR	< 6 time points
70	66 Patients / AR	< 6 time points
71	66 Patients / AR	< 6 time points

5.1.2.1 Autoregressive (AR1) Structure

There were 69 subjects and total of 618 time points for the dataset that was used for a GEE with an AR1 correlation structure. The relationship between logarithmic FIMS scores and ADS scores were assessed univariately. As shown below (Table 15), there is not an association between ADS and FIMS scores.

Table 15: Relationship between FIMS and ADS Scores

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	2.859	.0585	2.744	2.974	2384.738	1	.000
ADS	-.019	.0111	-.041	.002	3.026	1	.082

To assess which of the other variables are important predictors the rest of the variables were run univariately. The following variables were significant, FIMSMonth (time), race, current use of ChEIs or memantine, residence, history of alcohol use, and FCI score. The parameter estimates for these variables and ADS score are included in Table 16.

Table 16: Autoregressive Parameter Estimates

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	3.559	.3781	2.818	4.300	88.598	1	.000
FIMSMonth	-.015	.0023	-.019	-.010	39.356	1	.000
[ChEIMemantine=0]	.252	.1056	.045	.459	5.686	1	.017
[ChEIMemantine=1]	.205	.1178	-.026	.436	3.016	1	.082
[ChEIMemantine=2]	0[a]	.	.	.	.	.	.
[Race=1]	-.574	.0825	-.735	-.412	48.423	1	.000
[Race=2]	-.460	.1377	-.730	-.190	11.143	1	.001
[Race=3]	-.220	.1457	-.506	.065	2.290	1	.130
[Race=5]	0[a]	.	.	.	.	.	.
[Alcohol=0]	-.545	.3606	-1.252	.161	2.287	1	.130
[Alcohol=1]	-.500	.3425	-1.171	.171	2.131	1	.144
[Alcohol=2]	-.450	.3541	-1.144	.244	1.616	1	.204
[Alcohol=9]	0[a]	.	.	.	.	.	.
[Residence=1]	.415	.1667	.089	.742	6.211	1	.013
[Residence=2]	.556	.1602	.242	.870	12.066	1	.001
[Residence=3]	.048	.1676	-.281	.376	.082	1	.775
[Residence=4]	.229	.0996	.034	.424	5.282	1	.022
[Residence=9]	0[a]	.	.	.	.	.	.
ADS	-.009	.0102	-.029	.011	.773	1	.379
FCI	.018	.0098	-.001	.037	3.264	1	.071
(Scale)	.215						

Model fit is assessed by the quasi log likelihood under the independence criterion (QIC). The QIC is similar to the maximum likelihood function used in GEE. The QIC offers a rough guide of goodness of fit and can be used to compare nested models when choosing the best subset of predictors (Norusis, 2008). A model with a QIC that is smaller reflects that it is more effective at predicting than a model with a larger QIC (Norusis, 2008). Models with different predictor variables cannot be compared to each other using the QIC, only the models with different correlation structures and the same predictors. In the model displayed in Table 16, the QIC was 250.65. The QICs for the five models is located in Table 25.

5.1.2.2 Exchangeable Structure – 79 Patient Dataset

The second correlation structure evaluated was exchangeable with 79 patients, followed by the 5-dependent correlation structure. This 79 patient dataset includes all patients with at least two time points. Then both structures were run using the dataset with only 66 patients. This dataset includes only those with at least six time points. The description of the patients who were excluded and why are located in Table 14.

When the exchangeable results are reviewed, there are 1131 observations included without any missing data. The relationship between logarithmic FIMS scores and ADS scores were assessed univariately. As shown below (Table 17), there is not an association between ADS and FIMS scores.

Table 17: Exchangeable Structure – Relationship between FIMS and ADS Scores for 79 Patients

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	2.929	.0882	2.756	3.101	1102.166	1	.000
ADS	-.030	.0234	-.076	.016	1.676	1	.195

To assess which of the other variables are important predictors the rest of the variables were run univariately. The following variables were significant, FIMSMonth (time), race, marital status, length of stay (LOS), and residence. The parameter estimates for these variables and ADS score are included in Table 18. Marital status and LOS are no longer significant in this total model, but remain as they were univariately significant with the logarithmic transformation of FIMS score. Additionally, increased LOS is known to be associated with poorer outcomes.

Table 18: Exchangeable Structure Model for 79 Patients

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	3.299	.2895	2.732	3.867	129.852	1	.000
[Race=1]	-.411	.2026	-.808	-.014	4.119	1	.042
[Race=2]	-.245	.2083	-.653	.164	1.380	1	.240
[Race=3]	.200	.2159	-.224	.623	.854	1	.355
[Race=4]	.352	.2632	-.163	.868	1.793	1	.181
[Race=5]	0[a]	.	.	.	.	.	.
[MaritalStatus=1]	-.232	.2002	-.624	.160	1.343	1	.247

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
[MaritalStatus=2]	-.076	.2688	-.603	.451	.079	1	.778
[MaritalStatus=3]	-.311	.2066	-.716	.094	2.272	1	.132
[MaritalStatus=4]	-.220	.2247	-.660	.221	.958	1	.328
[MaritalStatus=5]	-.457	.2679	-.982	.069	2.903	1	.088
[MaritalStatus=9]	0[a]	.	.	.	.	.	.
[Residence=1]	.527	.1725	.189	.865	9.325	1	.002
[Residence=2]	.699	.1488	.407	.991	22.048	1	.000
[Residence=3]	.044	.1664	-.282	.370	.070	1	.791
[Residence=4]	.208	.0911	.030	.387	5.224	1	.022
[Residence=9]	0[a]	.	.	.	.	.	.
FIMSMonth	-.014	.0024	-.019	-.010	34.970	1	.000
ADS	-.023	.0178	-.058	.012	1.723	1	.189
LOS	5.871E-5	6.5490E-5	-6.965E-5	.000	.804	1	.370
(Scale)	.224						

5.1.2.3 5-Dependent Structure – 79 Patient Dataset

When the 5-dependent results are reviewed, there are 1131 observations included without any missing data. The relationship between logarithmic FIMS scores and ADS scores were assessed univariately. As shown below (Table 19), there is not an association between ADS and FIMS scores.

Table 19: 5-Dependent Structure – Relationship between FIMS and ADS Scores for 79 Patients

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	2.790	.0628	2.667	2.913	1973.088	1	.000
ADS	.005	.0130	-.021	.030	.122	1	.727

To assess which of the other variables are important predictors the rest of the variables were run univariately. The following variables were significant, FIMSMonth (time), residence, history of smoking and alcohol use, race, and length of stay (LOS). The parameter estimates for these variables and ADS score are included in Table 20. History of smoking and alcohol use, and LOS are no longer significant in this total model, but remain as they were univariately significant with the logarithmic transformation of FIMS score. Additionally, history of smoking, and alcohol, and increased LOS are known to be associated with poorer outcomes.

When the exchangeable and the 5-dependent reduced 2 models are compared the QICs are 489.38 and 451.31, respectively. Based on the goodness of fit, the 5-dependent is a better model when the 79 patient dataset is used.

Table 20: 5-Dependent Structure Model for 79 Patients

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	3.517	.2765	2.975	4.059	161.814	1	.000
[Race=1]	-.690	.0647	-.817	-.563	113.879	1	.000
[Race=2]	-.524	.0989	-.718	-.331	28.141	1	.000
[Race=3]	.029	.1624	-.290	.347	.031	1	.861
[Race=4]	.211	.1423	-.068	.490	2.200	1	.138
[Race=5]	0[a]	.	.	.	.	.	.
[Residence=1]	.515	.1703	.181	.848	9.131	1	.003
[Residence=2]	.559	.1384	.288	.831	16.336	1	.000
[Residence=3]	.086	.1616	-.231	.402	.281	1	.596
[Residence=4]	.224	.0993	.030	.419	5.104	1	.024
[Residence=9]	0[a]	.	.	.	.	.	.
[Smoking=0]	-.036	.2855	-.596	.523	.016	1	.899
[Smoking=1]	.230	.3112	-.380	.840	.545	1	.461
[Smoking=2]	.014	.2869	-.548	.576	.002	1	.961
[Smoking=9]	0[a]	.	.	.	.	.	.
[Alcohol=0]	-.332	.3486	-1.015	.351	.907	1	.341
[Alcohol=1]	-.385	.3334	-1.038	.269	1.331	1	.249
[Alcohol=2]	-.249	.3343	-.904	.406	.555	1	.456
[Alcohol=9]	0[a]	.	.	.	.	.	.
FIMSMonth	-.014	.0028	-.020	-.009	25.362	1	.000
ADS	.016	.0128	-.009	.042	1.635	1	.201
LOS	8.434E-5	5.9287E-5	-3.186E-5	.000	2.024	1	.155
(Scale)	.208						

5.1.2.4 Exchangeable Structure – 66 Patient Dataset

When the exchangeable results for the smaller dataset are reviewed, there are 1087 observations included without any missing data. The relationship between logarithmic FIMS scores and ADS scores were assessed univariately. As shown below (Table 21), there is not an association between ADS and FIMS scores.

Table 21: Exchangeable Structure – Relationship between FIMS and ADS Scores for 66 Patients

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	2.866	.0894	2.691	3.041	1027.506	1	.000
ADS	-.031	.0235	-.077	.016	1.691	1	.193

To assess which of the other variables are important predictors the rest of the variables were run univariately. The following variables were significant, FIMSMonth (time), FCI score, history of smoking and alcohol use, race, residence, and current use of ChEIs or memantine. The parameter estimates for these variables and ADS score are included in Table 22. History of smoking and use of ChEIs and memantine are no longer significant in this total model, but remain as they were univariately significant with the logarithmic transformation of FIMS score. Additionally, history of smoking is known to be associated with poorer outcomes.

Table 22: Exchangeable Structure Model for 66 Patients

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	3.387	.3172	2.765	4.009	114.018	1	.000
FCI	.036	.0096	.017	.055	14.096	1	.000
[Race=1]	-.433	.0982	-.626	-.241	19.474	1	.000
[Race=2]	-.335	.1547	-.638	-.031	4.681	1	.030
[Race=3]	.243	.1898	-.129	.615	1.640	1	.200
[Race=5]	0[a]	.	.	.	.	.	.
[ChEIMemantine=0]	.014	.1439	-.268	.296	.009	1	.924
[ChEIMemantine=1]	-.055	.1533	-.356	.245	.130	1	.719
[ChEIMemantine=2]	0[a]	.	.	.	.	.	.
[Smoking=0]	.227	.2425	-.248	.703	.878	1	.349
[Smoking=1]	.541	.2657	.021	1.062	4.152	1	.042
[Smoking=2]	.258	.2539	-.239	.756	1.035	1	.309
[Smoking=9]	0[a]	.	.	.	.	.	.
[Residence=1]	.490	.2540	-.008	.988	3.723	1	.054
[Residence=2]	.600	.1894	.229	.972	10.038	1	.002
[Residence=3]	.027	.2507	-.464	.519	.012	1	.913
[Residence=4]	.219	.1577	-.090	.528	1.931	1	.165
[Residence=9]	0[a]	.	.	.	.	.	.
[Alcohol=0]	-.574	.2742	-1.111	-.036	4.380	1	.036
[Alcohol=1]	-.684	.2261	-1.128	-.241	9.163	1	.002
[Alcohol=2]	-.527	.2599	-1.037	-.018	4.114	1	.043
[Alcohol=9]	0[a]	.	.	.	.	.	.
ADS	-.026	.0183	-.062	.010	2.070	1	.150
FIMSMonth	-.014	.0024	-.019	-.009	35.340	1	.000
(Scale)	.221						

5.1.2.5 5-Dependent Structure – 66 Patient Dataset

When the 5-dependent results for the smaller dataset are reviewed, there are 1087 observations included without any missing data. The relationship between logarithmic FIMS scores and ADS scores were assessed univariately. As shown below (Table 23), there is not an association between ADS and FIMS scores.

Table 23: 5-Dependent Structure – Relationship between FIMS and ADS Scores for 66 Patients

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	2.753	.0641	2.628	2.879	1845.427	1	.000
ADS	.005	.0132	-.021	.031	.136	1	.712

To assess which of the other variables are important predictors the rest of the variables were run univariately. The following variables were significant, FIMSMonth (time), FCI score, history of smoking and alcohol use, race, residence, and current use of ChEIs or memantine. The parameter estimates for these variables and ADS score are included in Table 24. All of the predictors except for time and race were no longer significant in the combined model. They were left in as they had a significant relationship with FIMS score and many are known to be associated with worsening outcomes in dementia.

When the exchangeable and the 5-dependent reduced 2 models are compared the QIC is 500.14 and 420.58, respectively. Based on the goodness of fit, the 5-dependent is a better model.

When all five models are compared and their QIC's are reviewed, Table 25, the autoregressive correlation structure is the best, with the lowest QIC that is at least half the other models.

Table 24: 5-Dependent Structure Model for 66 Patients

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	3.421	.2984	2.837	4.006	131.505	1	.000
FCI	.010	.0117	-.013	.033	.769	1	.380
[ChEIMemantine=0]	.213	.1044	.008	.418	4.154	1	.042
[ChEIMemantine=1]	.189	.1124	-.031	.410	2.838	1	.092
[ChEIMemantine=2]	0[a]	.	.	.	.	.	.
[Race=1]	-.634	.0825	-.795	-.472	58.975	1	.000
[Race=2]	-.464	.1292	-.717	-.211	12.911	1	.000
[Race=3]	-.048	.1766	-.394	.298	.074	1	.786
[Race=5]	0[a]	.	.	.	.	.	.
[Residence=1]	.324	.1967	-.062	.709	2.709	1	.100
[Residence=2]	.325	.1667	-.002	.652	3.802	1	.051
[Residence=3]	-.106	.1937	-.486	.273	.301	1	.583
[Residence=4]	.090	.1147	-.135	.315	.617	1	.432
[Residence=9]	0[a]	.	.	.	.	.	.
[Smoking=0]	.270	.2666	-.253	.792	1.024	1	.312
[Smoking=1]	.399	.2782	-.146	.944	2.060	1	.151
[Smoking=2]	.317	.2751	-.222	.856	1.328	1	.249
[Smoking=9]	0[a]	.	.	.	.	.	.
[Alcohol=0]	-.611	.2864	-1.173	-.050	4.552	1	.033
[Alcohol=1]	-.587	.2469	-1.071	-.103	5.641	1	.018
[Alcohol=2]	-.505	.2727	-1.040	.029	3.436	1	.064
[Alcohol=9]	0[a]	.	.	.	.	.	.
ADS	.020	.0136	-.007	.046	2.079	1	.149
FIMSMonth	-.012	.0023	-.017	-.008	29.370	1	.000

Table 25: Goodness of Fit for Five Models

Model	Goodness of Fit (QIC)
Autoregressive	250.65
Exchangeable (79 patients)	489.38
5-Dependent (79 patients)	451.31
Exchangeable (66 patients)	500.14
5-Dependent (66 patients)	420.58

5.1.3 Cognitive Outcomes

For the secondary outcome of cognition, the exchangeable and autoregressive structures were used. Exchangeable structure was run using the dataset with 66 patients as this produced a better model compared to the one that used all 79 patients. The autoregressive structure was run using the dataset with 69 patients with time measured quarterly. This was based on the fact that these are the two most common structures used for binary data (Lee et al, 2007).

When the model was run using the datasets, there was an error obtained relating to convergence. Therefore, a correlation table for all of the variables and the outcome of cognition was run. This table displayed a significant correlation of greater than 0.5 for LOS and FIMS Month. As a result LOS was removed and the analysis was re-run. The same error message relating to the inability of the model to reach convergence appeared. It was then hypothesized that the model was over parameterized; therefore each variable was individually run against the outcome of cognition.

The relationship between cognitive outcomes and ADS scores using the exchangeable and autoregressive structures are located in Tables 26.

Table 26: Relationship between Cognition and ADS Scores

Exchangeable Structure

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	-.172	.2196	-.602	.259	.611	1	.435
ADS	-.033	.0554	-.142	.076	.351	1	.553

AR1 Structure

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	-.400	.1893	-.771	-.029	4.469	1	.035
ADS	.011	.0428	-.073	.095	.070	1	.792

The relationship is shown above and there is not an association between ADS scores and cognition using either of the two structures. There were other variables that were significant predictors of change in cognition for the exchangeable structure. These included race, residence, presence of constipation, and time (FIMS Month). The same procedure was done for the AR1 structure and the significant variables were presence of constipation and time. The parameter estimates for both structures with only the significant variables are located in Table 27. The goodness-of-fit tests were evaluated between the two structures. Again, the autoregressive structure had a smaller QIC of 1187.83 compared to 1973.33 for the exchangeable structure.

The model that predicts the outcome variable of change in cognition is the autoregressive correlation structure. The effects that were significant and therefore predictive of the outcome include time and presence of constipation on admission.

Table 27: Cognitive Outcome – AR1 and Exchangeable Structure

Parameter Estimates for Significant Variables for the AR1 Structure

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	-.132	.1966	-.517	.253	.450	1	.502
[Constipation=1]	.927	.2719	.394	1.460	11.630	1	.001
[Constipation=0]	0[a]	.	.	.	.	.	.
FIMSMonth	-.031	.0072	-.045	-.017	18.905	1	.000

Parameter Estimates for Significant Variables for Exchangeable Structure

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	-1.172	.2693	-1.700	-.644	18.929	1	.000
[Race=3]	-2.140	.2131	-2.558	-1.723	100.875	1	.000
[Race=2]	-.296	.2631	-.812	.219	1.269	1	.260
[Race=1]	-.366	.2583	-.872	.141	2.003	1	.157
[Race=0]	0[a]	.	.	.	.	.	.
[Residence=4]	1.371	.2543	.872	1.869	29.055	1	.000
[Residence=3]	.991	.2887	.425	1.557	11.779	1	.001
[Residence=2]	1.366	.3983	.585	2.146	11.757	1	.001
[Residence=1]	1.361	.3721	.632	2.090	13.378	1	.000
[Residence=0]	0[a]	.	.	.	.	.	.
[Constipation=1]	.962	.2865	.400	1.524	11.274	1	.001
[Constipation=0]	0[a]	.	.	.	.	.	.
LOS	-.001	.0002	-.001	.000	10.693	1	.001

5.1.4 Behavioral Outcomes

The other secondary outcome of behavior was also evaluated using the exchangeable structure and autoregressive structures. The same warnings associated with cognition emerged when the model was run with all of the variables. Therefore each variable was run univariately with behavior and then the significant variables were run together.

The relationship between cognitive outcomes and ADS scores using the exchangeable and autoregressive structures are located in Tables 28.

Table 28: Relationship between Behavior and ADS Scores

Exchangeable Structure

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	.853	.1971	.467	1.239	18.733	1	.000
ADS	-.001	.0497	-.098	.096	.000	1	.983

AR1 Structure

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	.875	.2133	.457	1.293	16.820	1	.000
ADS	.005	.0538	-.100	.111	.010	1	.921

The relationship is shown above and there is not an association between ADS scores and behavior using either of the two structures. There were other variables that were significant predictors of change in behavior. The parameter estimates for the autoregressive and exchangeable structures are located in Table 29. For the AR structure the following were the significant variables, time, race, age, presence of constipation, and residence. For the exchangeable structure the significant variables were time, race, marital status, smoking and presence of constipation.

The goodness-of-fit tests were evaluated between the two structures. Again, the autoregressive structure had a smaller QIC of 1465.44 compared to 2489.34 for the exchangeable structure.

Table 29: Behavioral Outcomes using AR1 and Exchangeable Structure

Parameter Estimates for Significant Variables for AR1 Structures

Parameter			95% Wald Confidence Interval		Hypothesis Test		
	B	Std. Error	Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	3.914	1.6627	.655	7.173	5.541	1	.019
[Constipation=1]	.683	.3544	-.012	1.377	3.713	1	.054
[Constipation=0]	0[a]	.	.	.	.	.	.
[Residence=4]	1.678	.2774	1.135	2.222	36.611	1	.000
[Residence=3]	1.028	.3365	.368	1.687	9.331	1	.002
[Residence=2]	1.560	.5475	.487	2.633	8.122	1	.004
[Residence=1]	.987	.3773	.247	1.726	6.840	1	.009
[Residence=0]	0[a]	.	.	.	.	.	.
[Race=3]	-2.287	.2624	-2.801	-1.772	75.932	1	.000
[Race=2]	.252	.3312	-.398	.901	.577	1	.447
[Race=1]	.817	.2470	.333	1.301	10.942	1	.001
[Race=0]	0[a]	.	.	.	.	.	.
Age	-.055	.0237	-.102	-.009	5.396	1	.020
FIMSMonth	-.024	.0056	-.035	-.013	18.331	1	.000

Parameter Estimates for Significant Variables for Exchangeable Structure

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	-3.289	.7094	-4.679	-1.899	21.495	1	.000
[Race=0]	5.212	.4731	4.285	6.139	121.382	1	.000
[Race=1]	2.652	.2170	2.227	3.078	149.384	1	.000
[Race=2]	3.141	.3459	2.463	3.819	82.465	1	.000
[Race=3]	0[a]	.	.	.	.	.	.
[MaritalStatus=0]	1.134	.9743	-.776	3.043	1.354	1	.245
[MaritalStatus=1]	1.397	.4206	.573	2.222	11.031	1	.001
[MaritalStatus=2]	.547	.3471	-.133	1.227	2.482	1	.115
[MaritalStatus=3]	.905	.4802	-.036	1.846	3.549	1	.060
[MaritalStatus=4]	1.175	.5513	.094	2.255	4.540	1	.033
[MaritalStatus=5]	0[a]	.	.	.	.	.	.
[Smoking=0]	1.006	.3447	.331	1.682	8.526	1	.004
[Smoking=1]	.611	.5177	-.404	1.625	1.392	1	.238
[Smoking=2]	1.489	.4168	.672	2.306	12.761	1	.000
[Smoking=3]	0[a]	.	.	.	.	.	.
[Constipation=0]	-.567	.2393	-1.036	-.098	5.615	1	.018
[Constipation=1]	0[a]	.	.	.	.	.	.
FIMSMonth	-.024	.0064	-.037	-.012	14.697	1	.000

5.1.5 Summary of Results

In this study there are three outcomes of interest with the use of AC medications. Function, was the primary outcome of interest and several models using different sized datasets were compared. By altering the recorded arrangement of time from the first and last consecutive six months with time measured quarterly between these time periods, to a more uniform time structure made a difference in determining the model with the best predictive ability. This structure with the best predictive ability was the AR1 one, based on its QIC value.

An association between anticholinergic burden, using ADS scores, and function was not found. The p-values shown in Tables 15-23, demonstrate the burden was not statistically associated with function. The p-value in Table 15, using the AR1 structure, suggested that burden might have an effect on function, but when the other significant variables were included in an analysis, the variable became not significant.

There were other variables that were associated with function using the AR1 structure. These include, time (FIMSMonth), race, current use of ChEIs or memantine, residence, history of alcohol use, and FCI score. Higher FIMS scores or improved function was negatively associated with time (-.02) and White (-.57) or Black (-.46) race. The higher functional scores were positively associated with the use of memantine or a ChEIs (.21) and living at home (with or without assistance) prior to admission to PGH (.556 and .415). The other variables were no longer significant in the combined model. Individually, prior use of alcohol (-.67) had a negative relationship with higher function. Additionally, FCI (.03) had a positive association with increased FIMS scores. The individual associations between these six variables and function were all highly significant.

The second outcome of interest was cognition, which was a binomial variable. There were two correlation structures that were used to identify the best model for this outcome. Exchangeable and autoregressive were the two structures compared. The results identified that the autoregressive was the better model

Burden was not associated with cognitive outcomes. The variable was highly insignificant as a predictor of change in cognition. The variables that were statistically significant as predictors of change in cognition include the presence of constipation on admission and time. Time (-.03) was

negatively associated and the presence of constipation (.93) was positively associated with change in cognition. This is shown in Table 27.

The third outcome of interest was behavior, also a binomial variable. Two structures, exchangeable and autoregressive were compared. The autoregressive structure was again the more robust of the two and produced a better model. In this model, burden was not associated with change in behavior. There were other variables that were statistically significant with change in behavior and these include time, race, age, presence of constipation, and residence. Time was negatively (-.02) associated with change in behavior as was age (-.06) and White race (-.79). Presence of constipation on admission (.68) and any residence prior to admission was positively associated with a change in behavior as shown in Table 29.

When all of the variables are considered, time is a predictor of all three outcomes. Additionally, there other variables predictive of two of the outcomes including race, residence, and presence of constipation on admission.

Chapter 6

Discussion and Conclusions

6.1 Discussion

Older adults are at increased risk of developing negative side effects and adverse events from medications, especially those with AC activity. This is suggested to be true for older adults with dementia as well. There is an increasing amount of evidence that consequences including increased cognitive impairment, physical impairment and rapid functional decline are associated with drugs that have a high AC burden in patients with dementia (Kowlanski et al, 2009).

Several studies have shown the efficacy of using non-invasive tools to calculate AC burden in older adults. Carnahan et al developed the Anticholinergic Drug Scale (ADS) that calculates AC burden based on a rating scale that categorizes medications as "3" known to be highly AC to "0" no known AC effects (Carnahan et al, 2006). This tool was used in this study to calculate burden.

This study evaluated the effects of burden on function, cognition, and behavior in moderate to severe dementia patients in a state run psychiatric hospital. Few studies have investigated the effects of AC burden on function in moderate to severe AD patients. This is the only study, to the knowledge of the author, to specifically evaluate these effects in a state run hospitalized

setting. Furthermore, few studies have evaluated these effects on behavior and cognition as well in this patient population. This study did not find a statistical association between AC burden and functional impairment. Additionally, a statistical association was not seen with AC burden and either cognitive or behavioral outcomes. One possible reason for this outcome could be specific drugs that are not considered to be highly AC according to the ADS but are known to cause functional impairment in older adults and dementia patients. Benzodiazepines and antipsychotics have been shown to be associated with negative outcomes in older adults and those with dementia (Hilmer et al, 2009), but only a few in each class have AC properties according to the SAA assays.

6.2 Burden Effects on Function

Much of the evidence of AC burden being associated with poorer outcomes is in older adults without dementia. This is discussed in section 1.2, where much of the evidence is from studies in psychiatrically stable older adults. Furthermore, some of the scales used to quantify burden use older adults without dementia or cognitive impairment. This may be one reason why the current study failed to show an association between burden and outcomes. The studies conducted in cognitively stable and community residing older adults are an important starting point as much of the inappropriate or AC medication use is not exclusive to this population. It is also not uncommon in nursing homes and hospitals where there are an increasing number of moderate to severe dementia patients. In a study by Landi et al, inappropriate medications including some that have AC properties were associated with impaired physical performance, muscle strength and functional status (Landi et al, 2007). Inappropriate medications have been shown to increase the risk of falls (Nebes et al, 2007) and therefore higher morbidity and

mortality in an already vulnerable population. There are few studies that have investigated the association between AC burden and function in dementia patients. One such study by Sink et al, found a decline in higher functioning dementia patients taking AC medications and functional impairment. The decline in the seven components of the activities of daily living (ADLs) was 1.62 in patients taking tolterodine and oxybutynin compared 1.08 for those not taking the two AC medications (Sink et al, 2008). The two medications used in the study are level 3 AC medications. The most commonly used medications in this study of moderate to severe dementia patients at PGH, used medications that were levels 1 and 2 medications. Additionally, while statistical significance was not determined for the association between AC burden and function, the results are inconclusive based on the limitations of the study and the limited amount of evidence in the literature.

6.3 Other Effects on Function

In this study, the model found that there are other variables that affect function including time, race, current use of ChEIs or memantine, residence, history of alcohol use, and FCI score. In this study impaired function refers to decreased FIMS scores, therefore some of the relationships between the variables and the outcome are not as expected. Higher FIMS scores or improved function was negatively associated with time, White or Black race, and use of alcohol. As time increased function decreased. Also, decreased functioning was associated with White or Black races. This may not be an accurate relationship as there were only three patients who were not classified as White or Black. Lastly, decreased function was associated with current or previous alcohol use. Positive associations were found with the use of memantine or a ChEIs, living at home (with or without assistance) prior to admission to PGH, and FCI. Higher functioning was associated with patients who used memantine or ChEIs.

Additionally, those patients that lived at home prior to being admitted to PGH were associated with higher functional scores. The last association was with FCI, the higher the functioning the higher number of chronic diseases that affect function. This association is difficult to follow, as more chronic diseases would be expected to decrease functioning not increase it.

6.4 Effects on Cognition and Behavior

There are numerous studies that have evaluated cognition in those older adults that have received AC medications. There are fewer studies in dementia adults compared to non-demented adults, but the results are the same. Increased AC burden increases cognitive impairment, which was described in section 1.2. This study, however, did not find an association between burden and worsening cognition. This is counterintuitive especially when the patients had an average burden score of 3.0. This is a high score compared to a study by Boustani et al, where the average burden scores were 1.7 using the ACB, a tool similar to the ADS, in 3013 older adults (Boustani et al, 2008). Another study, by Kowlanski et al, also had a high burden score of 2.55 in dementia patients and did not find an association between engagement and burden (Kowlanski et al, 2009). The study by Sink et al also did not find an association between burden and cognition (Sink et al, 2008). There are several potential reasons for this including the use of the ADS to quantify burden, the use of subjective measures of cognition quantified as change or no change, the more severe stress of dementia experienced by these patients, and possibly the low sample size. These are described in more detail in section 6.5.

Behavioral problems typically increase as dementia progresses (1), but few studies have investigated the increased behavioral problems that are associated with AC medications. The

studies that discuss behavioral problems in dementia patients, usually do so in the context of treating them (Edell et al, 2001; Adams et al, 2003). These studies investigate the use of antipsychotic medications and their benefits on behavior. Some of these antipsychotics have AC properties including olanzapine, clozapine, and thioridazine. It would seem that if AC medications impair function and cognition, then behavior would be impaired as well. In this study there was not an association between burden and behavior. The only study that investigated this relationship did so through engagement (Kowlanski et al, 2009). Where the dementia participants with increased burden did not have an association with worsening engagement, specifically, increased sleeping, decreased activity, and increased "doing nothing." Future research will need to determine if there is a link between behavior and AC burden in dementia patients.

6.5 Limitations of Study

The lack of ability to identify an association, if it exists, between function, cognition, and behavior and AC burden may be explained by several factors related to the design of this study and the patient population who participated. The first is that all of the participants were at different stages in their disease when they were admitted to PGH. Severe disease is associated with greater functional, cognitive, and behavioral deficits that may mask or provide more influence on these outcomes than AC burden. This was noted in a study by Sink et al that did not find an association between AC drug use and cognition in more severe dementia patients (Sink et al, 2008).

A second possibility is the source of the data. Nursing notes in ht medical record are subjective in assessing cognition and behavior. The inter- and intra-variability among nurses makes it

inherent that there will be some incorrect interpretations as to the definition of worsening behavior. In one instance, a patient had been moved from one unit to another due to the behavioral problems. The notes from the original unit showed worsening behavior, but when transferred the patient's behavior stabilized with no major improvement or worsening. Also, there was not a widely-used definition employed by the investigator (S. Dharia) to determine change. The use of only one investigator to decipher the notes reduced any bias in the interpretation of them. Hand-writing, was an additional issue as it made some notes difficult to interpret. There are several tools for cognition and behavior in dementia, such as the Alzheimer Disease Assessment Scale-Cognitive (ADAS-Cog) (Rosen et al, 1984) or the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) (Reisberg et al, 1987), but most are not appropriate in this setting. Several are lengthy and time-consuming or require the nurse or aide to ask several questions or interview the patient. Tools such as the Severe Impairment Battery (SIB) may be appropriate in this setting (Albert et al, 1992). Future research to develop a tool that allows for the nurse or aide to use direct observation to assess behavior and cognition and takes a short amount of time to fill out would be ideal and reduce any bias.

There are some limitations of using the ADS. This scale may not fully capture AC burden as it does not take into account dose. A study that evaluated the relationship between AC burden and decrease engagement in dementia patients used a similar tool to quantify burden, the Anticholinergic Burden scale (ACB), did not find an association with burden (Kowlanski et al, 2009). One limitation that was noted in the study was the limited precision in the categorization of the AC activity by using the 3-point scale (Kowlanski et al, 2009). Additionally, the individual differences in absorption, distribution, metabolism and excretion

are considerable. Using a scale such as the ADS does not take this into account and may explain the non-statistically significant result. Also, not taking into consideration dose may affect the outcome. Furthermore, there are several changes in a patient's medications when an individual is admitted to PGH in order to stabilize them. Many of the medications used are antipsychotics that may not be on the ADS scale, even though, these drugs are known to cause impaired cognition, behavior and function in older adults (Hilmer et al, 2009). Lastly, there are several methods for estimating burden, all of which have their strengths and weaknesses, with no ideal one (Carriere et al, 2009).

Another factor may have been the small number of patients in the study. A larger sample may provide a significant association. The sample size calculation performed determined that 436 patients were needed in order to obtain 80% power in this study. Increasing the number of patients would have been difficult in this situation as each of the five state run mental health hospitals do not use the FIMS as a functional assessment tool. Additionally, not all of the hospitals have geriatric centered care.

An additional limitation of this study is the observational nature of the research as cause and effect cannot be established. While there is much speculation as to the strength of evidence from an observational study, an article found that the average results from randomized, controlled studies overestimated the magnitude of the associations and the well-designed observational ones did not (Concato et al, 2000). Furthermore, the observational studies evaluated, had less variability in the estimates than did the RCTs on the same cardiovascular topic. Therefore, the observational design might not be a true limitation of the study.

Much of the dementia research concerning the use of medications with AC properties is performed in AD patients specifically. In this study the original design was to include only AD patients, but due to the low number all dementia patients were included. AD patients appear to be at greater risk of negative effects using AC medications due to the etiology of the disease and the large proportion of this form of dementia compared to the others. Yet all dementia patients are vulnerable due the significant cognitive impairment associated with the disease.

6.6 Strengths

Some of the strengths of this study include the data source. The use of medical charts provides much more information about a participant's health, medical, and pharmacy data compared to a claims database. Pharmacy or hospital claims data are sometimes used as an information source for studies. In the preliminary research study, section 3.1, the first study described used a procedure and diagnosis specific database that while large in size did not include all of the pertinent information.

Additionally, the longitudinal nature of the research is an advantage. Compared to a cross-sectional method, this method allows for evaluation of an outcome over time and for a truer representation of the relationship between various effects and the outcomes. It also allows for stronger associations to be made between outcomes of interest and specific variables.

The use of only one student to collect all of the data, except one patient, minimizes any inter-rater variability that may have occurred. In addition, when interpreting the subjective nursing notes, using only one rater minimized any bias.

Lastly, moderate to severe dementia patients are not widely studied, especially those in state-run psychiatric hospitals. This study provided knowledge on an underrepresented and exceedingly vulnerable population due to their disease and special care.

6.7 Future Directions

The majority of the research in the area of AC burden is conducted in older adults that do not suffer from dementia. What little literature there is on dementia and AC burden is mostly in the form of case studies or observational studies. Additionally, many are focused on cognitive outcomes. Future research should make use of experimental designs, specifically an interventional study or make use of national disease databases. This interventional study should assess the change or improvement in functional, cognitive, and behavioral impairment caused by AC medications as dementia patients are removed from potentially inappropriate medications. Furthermore, different levels of burden should be included, to determine if lower burden causes less harm than more burden. The intervention should be to remove the participants from the AC medications and compare them to those who are still currently taking the medications over a period of time. Outcomes should include at least behavior, function, and cognition. A randomized clinical trial (RCT) will provide added evidence as to the negative effects or no effects of AC burden on dementia patients. Moreover, an RCT will provide a better estimate of the potential causal relationship between AC burden and outcomes. Additionally, the use of a large disease database will have to wait until they have been completed as they are still in the process of being developed. One potential problem with this proposed study is the recruitment of patients. As mentioned in sections 1.4 and 3.2, recruitment of older adults and those with dementia is a barrier to conducting research

including experimental and prospective observational studies. Overcoming this barrier is imperative to further research in the area of dementia.

6.8 Conclusions

The effect of AC medications on moderate to severe dementia patients is not fully understood. The minimal amount of literature on this association, suggests that AC burden may have negative consequences on function, cognition and behavior in dementia patients. This study provided inconclusive evidence to this current theory that AC burden negatively impacts function, cognition, and behavior in dementia patients. To further this area of research, overcoming recruitment barriers is essential.

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Appendix A: Patient Intake Form

Subject #: _____

Cognitive, Functional and Behavioral Outcomes Associated with Anticholinergic Drug use in Alzheimer's disease Patients Taking Cholinesterase Inhibitors

Participant Demographic Form: Please answer the following questions concerning the patient to the best of your ability. If you have concerns about any of the questions please let us know at the first visit.

1. Date of Birth (MM/DD/YYYY): _____
2. Age (in years): _____
3. Sex (check one):
   ___Male

   ___Female
4. Marital Status (check one):
   ___Married

   ___Single

   ___Divorce

   ___Other
5. Ethnicity (check one):
   ___White

   ___Black

   ___Hispanic

   ___Asian/Pacific Islander

   ___American Indian/Alaskan Native

   ___Other/Not Specified

6. Residence (check one):
   ___Home

   ___Assisted Living Facility

   ___Other

7. How long have you lived at your current residence:
   _____

8. Primary care doctor: _____

9. Have you ever participated in a study or clinical trial (check one):
   ___Yes

   ___No

10. Highest Grade Achieved (check one):
    ___Elementary School

    ___Middle School

    ___High School

    ___College

    ___Graduate

11. Current Smoker (check one):
    ___Yes

    ___No

If yes, how many years: ____

In addition, how many cigarettes per day: ____

12. If no, did you smoke previously (check one):
    ___Yes

    ___No

If yes, how long ago: ____

In addition, how many cigarettes per day: ____

13. Current Diagnoses (check as many as apply):

___Parkinson's Disease ___Diabetes

___Urinary Incontinence ___Thyroid Problems

___Abdominal Cramps ___Clots

___Diarrhea ___Depression

___Wear Eyeglasses ___Alcohol Problems

___Use Hearing Aids ___Seizures

___Vomiting ___Arthritis

___Nausea ___Cancer

___Loss of Appetite ___High Blood Pressure

___Increase Heart Rate ___Confusion

___High Cholesterol ___Head Trauma

___Heart Murmur ___Loss of Coordination

___Arrhythmias ___Dry Mouth

___Asthma ___Constipation

___Pneumonia ___Agitation

14. Do you have a family history of the following disorders or illnesses:
___Parkinson's Disease ___Alzheimer's Disease

___High Cholesterol ___Thyroid Problems

___Diabetes ___Anemia

___Cancer ___Arrhythmias

___High Blood Pressure ___Heart Murmur

15. When were you diagnosed with AD (MM/DD/YYYY): _____
16. Which medication for AD are you currently taking (check all that apply):
___Aricept

___Exelon

___Razadyne

___Namenda

17. How long have you been taking the above medication (years): _____

18. Were you previously on a different medication for AD (check one):
___Yes

___No

19. If yes, which one (check all that apply):
___Aricept

___Exelon

___Razadyne

___Namenda

20. Do you think your current AD medication is working (check one):
___Yes

___No

21. Please list all current medications (please back of this page if you run out of space):

Name	Indication	Route	Dosage	How often taken

22. Please list all current Supplements/Vitamins/Herbals/OTC (please back of this page if you run out of space):

Name	Indication	Route	Dosage	How taken

_____
_____
_____
_____

23. Do you think these medications are working (check one):
    ___Yes
    ___No

24. If not, please list which ones are not working:
    _____
_____
_____
_____
_____

25. Approximately how much is your annual out of pocket expenditure on medications and supplements : _____
26. What type of prescription drug insurance do you have (check all that apply):
    ___Medicare part D

    ___Medicaid

    ___Both

    ___Other

    If other, please indicate:
    _____

27. On how many days per week do you eat red meat: _____
28. What kind of physical exercise do you do (check all that apply):
    ___Aerobics

    ___Weight-lifting

    ___Walking

    ___Running/Jogging

    ___Cycling

    ___Swimming

    ___Other

    If other, please indicate:
    _____

29. What kinds of activities do you enjoy (examples - memory games, gardening, crossword puzzles): _____
_____
_____

Appendix B: Anticholinergic Drug Scale

Level 3 Drugs

Amitriptyline, dicyclomine, oxybutynin, atropine, dimenhydrinate, procyclidine, benztropine, diphenhydramine, promethazine, brompheniramine, doxepin, propantheline, carbinoxamine, flavoxate, protriptyline, chlorpheniramine, hydroxyzine, pyrilamine, chlorpromazine, hyoscyamine, scopolamine, clemastine, imipramine, thioridazine, clomipramine, meclizine, tolterodine, clozapine, nortriptyline, trihexyphenidyl, darifenacin, orphenadrine, trimipramine, desipramine

Level 2 Drugs

Carbamazepine, disopyramide, molindone, cimetidine, loxapine, oxcarbazepine, cyclobenzaprine, meperidine, pimozide, cyproheptadine, methotrimeprazine, ranitidine

Level 1 Drugs

Alprazolam, divalproex sodium, olanzapine, amantadine, estazolam, oxazepam, ampicillin, famotidine, oxycodone, azathioprine, fentanyl, pancuronium, bromocriptine, fluoxetine, paroxetine, captopril, fluphenazine, perphenazine, cefamandole, flurazepam, phenelzine, cefoxitin, fluticasone-salmeterol, piperacillin, cephalothin, fluvoxamine, prednisolone, chlordiazepoxide, furosemide, prednisone, chlorthalidone, gentamicin, prochlorperazine, clindamycin, hydralazine, sertraline, clonazepam, hydrocortisone, temazepam, clorazepate, isosorbide, theophylline, codeine, isosorbide dinitrate, thiothixene, cortisone, isosorbide mononitrate, tramadol, cycloserine, ketotifen, ophthalmic triamcinolone, cyclosporine, loperamide, triamterene, dexamethasone, lorazepam, triazolam, diazepam, methylprednisolone, trifluoperazine, digitoxin, midazolam, valproic acid, digoxin, morphine, vancomycin, diltiazem, nifedipine, warfarin, dipyridamole, nizatidine,

Level 0 Drugs

Acarbose, acetaminophen, acetaminophen/dichloralphenazone/isometheptene, acetazolamide, acetic acid topical, acyclovir, adenosine, albuterol, alendronate, allopurinol, aluminum carbonate, aluminum hydroxide, amiloride, amiodarone, amlodipine, ammonium lactate

topical, amoxicillin, amoxicillin-clavulanate, anagrelide, anastrozole, anileridine, apraclonidine ophthalmic, ascorbic acid, aspirin, atenolol, atorvastatin, azithromycin, bacitracin ophthalmic, bacitracin topical, baclofen, balsam Peru topical, beclomethasone, beclomethasone nasal, benazepril, benzocaine topical, benzonatate, beta-carotene, betamethasone topical, betamethasone-clotrimazole topical, betaxolol ophthalmic, bethanechol, bicalutamide, bisacodyl, bismuth subsalicylate, bisoprolol, brimonidine ophthalmic, brinzolamide ophthalmic, budesonide, budesonide nasal, bumetanide, bupropion, buspirone, butabarbital, butalbital, caffeine, calamine topical, calcipotriene topical, calcitonin, calcitriol, calcium acetate, calcium and vitamin D, calcium carbonate, camphor-menthol topical, candesartan, carbachol ophthalmic,

carbamide peroxide otic, carbidopa, carisoprodol, carvedilol, casanthranol, casanthranoldocusate, cascara sagrada, castor oil, cefaclor, cefazolin, cefixime, ceftibuten, ceftriaxone, cefuroxime, elecoxib, cephalexin, cerivastatin, cetirizine, cetylpyridinium topical, chloral hydrate, chlorambucil, chlorhexidine topical, chlorothiazide, chlorpropamide, chlorzoxazone, cholestyramine, chondroitin, ciclopirox topical, cilastatin, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, clavulanate, clindamycin topical, clobazam, clodronate, clonidine, clopidogrel, clotrimazole, cloxacillin, colchicines, colestipol, collagenase topical, conjugated estrogens, cranberry, cromolyn, cyanocobalamin, cyclophosphamide, danazol, dantrolene, demeclocycline, desmopressin, desonide topical, desoximetasone topical, dexamethasone nasal, dexamethasone ophthalmic, dexamethasone topical, dextromethorphan, diclofenac, dienestrol topical, diflunisal, dihydroxyaluminum sodium carbonate, diphenoxylate, dipivefrin ophthalmic, dirithromycin, dobutamine, docusate, donepezil, dopamine, dorzolamide ophthalmic, doxazosin, doxycycline, duloxetine, econazole topical, edrophonium, enalapril, enoxaparin, entacapone, epoetin alfa, ergocalciferol, ergoloid mesylates, erythromycin, escitalopram, esomeprazole, esterified estrogens, estradiol, estradiol topical, estropipate, ethambutol, ethinyl estradiol, etidronate, etodolac, felbamate, felodipine, fenofibrate, ferrous gluconate, ferrous sulfate, fexofenadine, filgrastim, finasteride, flecainide, fluconazole, fludrocortisone, flumazenil, flunisolide, fluocinonide topical, fluoride topical, fluorometholone ophthalmic, flutamide, fluticasone, fluvastatin, folic acid, fosinopril, gabapentin, galantamine, gemfibrozil, gentamicin ophthalmic, gentamicin topical, ginkgo, glimepiride, glipizide, glucagons, glucosamine, glyburide, glycerin topical, guaifenesin, guanfacine, halcinonide topical, haloperidol, heparin, hydrochlorothiazide, hydrocodone, hydrocortisone ophthalmic, hydrocortisone otic, hydrocortisone topical, hydromorphone, hydroxychloroquine, hydroxypropyl, methylcellulose ophthalmic, hydroxyurea, ibuprofen, imipenem, indapamide, indomethacin, insulin, ipratropium, irbesartan, iron polysaccharide, isoniazid, isradipine, ketoconazole topical, ketoprofen, labetalol, lactase, lactulose, lamotrigine, lanolin-mineral oil topical, lansoprazole, latanoprost ophthalmic, leuprolide, levobunolol ophthalmic, levodopa, levofloxacin, levothyroxine, lidocaine, lindane topical, liothyronine, lisinopril, lithium, loratadine, losartan, loteprednol ophthalmic, lovastatin, LVP solution,

Lysine, Magnesium preparations, mannitol, medroxyprogesterone, megestrol, meprobamate, mesalamine, metaxalone, metformin, methazolamide, methenamine, methotrexate, methyclothiazide, methylcellulose, methyldopa, methylene blue, methylphenidate, methylprednisolone topical, methyltestosterone, metoclopramide, metolazone, metoprolol, metronidazole, mexiletine, miconazole topical, midodrine, mineral oil, minocycline, mirtazapine, misoprostol, moexipril, mometasone nasal, montelukast, moxifloxacin, multivitamin, mupirocin topical, nabumetone, nadolol, naloxone, naproxen, nateglinide, nefazodone, neomycin ophthalmic, niacin, nisoldipine, nitrofurantoin, nitroglycerin, norepinephrine, norfloxacin, nystatin, octreotide, ofloxacin, olopatadine ophthalmic, omeprazole, oxymetazoline nasal, pamidronate, pancrelipase, pantoprazole, papaverine, penicillin, pentoxifylline, pergolide, perindopril, permethrin topical, petrolatum topical, phenazopyridine, Phenobarbital, phenyl salicylate, phenylephrine, phenylpropanolamine, phenytoin, phytonadione, pilocarpine ophthalmic, pindolol, pioglitazone, pirbuterol, piroxicam, pivampicillin, polycarbophil, polyethylene glycol electrolyte solution, polymyxin B ophthalmic, potassium bicarbonate, potassium chloride, potassium citrate, pramipexole, pramoxine topical, pravastatin, prazosin, prednisolone ophthalmic, primidone, probenecid, procainamide, progesterone, propafenone, propoxyphene, propranolol, propylthiouracil, pseudoephedrine, psyllium, pyrazinamide, pyridostigmine, quetiapine, quinapril, quinidine, quinine, rabeprazole, raloxifene, ramipril, repaglinide, reserpine, rifampin, rimantadine, rimexolone ophthalmic, risedronate, risperidone, rofecoxib, ropinirole, rosiglitazone, salicylic acid topical, salmeterol, salsalate, selegiline, selenium sulfide topical, senna, silver sulfadiazine topical, simethicone, simvastatin, sodium bicarbonate, sodium chloride, sodium phosphate, sodium sulfacetamide ophthalmic, sotalol, spironolactone, succinylcholine, sucralfate, sulfamethizole, sulfamethoxazole, sulindac, tacrine, tamoxifen, tamsulosin, terazosin, terbinafine topical, terbutaline, terconazole topical, tetracycline, thiamine, thyroid desiccated, ticlopidine, timolol, tobramycin ophthalmic, tolbutamide, tolcapone, topiramate, torsemide, trandolapril, trazodone, triamcinolone nasal, triamcinolone topical, trichlormethiazide, triethanolamine, polypeptide, oleate otic, trimethoprim, troglitazone, trypsin, tuberculin purified protein derivative, ursodiol, valsartan, vecuronium, venlafaxine, verapamil, vitamin E, zafirlukast, zaleplon, zinc gluconate, zinc sulfate, zolpidem, zopiclone

Appendix C: PGH Letter of Consent

March 31, 2010

[Mr/Mrs. Patient/AR]

[Street Address]

[City, State ZIP]

RE: [Patient name/Reg. No.]

Dear [Mr./Mrs. Patient/AR]:

Piedmont Geriatric Hospital has been contacted by a Virginia Commonwealth University (VCU) graduate student, Sheetal Dharia, who is working toward her doctorate in Pharmacy. She is interested in using our data for a research project designed to evaluate the possible effects of the use of a combination of medications that are for health conditions other than Alzheimer's disease or dementia on the functional and cognitive status of people who have dementia.

The goals of this project are:

1) To better understand what happens when people with dementia take multiple medications

2) To improve how medications are used in the future for patients with dementia

The student is requesting access to medical and prescription information from the records of the above named patient. Any identifiable information such as name, date of birth, admission and discharge dates will not be collected or published for this project. We are notifying you in advance in order to give you an opportunity to agree or object to the record being accessed for this purpose.

Enclosed you will find a list of the information that will be collected, and an authorization form to sign if you wish to grant permission for this project. If, however, you object to participation in this research project, please simply write "I object" at the top of the form and leave the form unsigned. Please return the form in the enclosed envelope by **April 15, 2010**. If we have not received a response by April 19, 2010, we will interpret the lack of response to mean there is no objection**.** If you have concerns that you would like to discuss regarding this project, please contact me at (434)767-4411.

Sincerely,

Peggy S. Vaughan

Health Information Manager

Research Information Sheet

Focus of Research:	Evaluate possible effects of the combination of medications that are for health conditions other than Alzheimer's disease or dementia on the functional and cognitive status of people with dementia
Information Collecting:	▶ Medications ▶ Scores for thinking and functioning (Nursing documentation) ▶ Sex ▶ Marital Status ▶ Age ▶ Race/Ethnicity ▶ Length of Stay at Piedmont Geriatric Hospital ▶ Number of hospitalizations at Piedmont Geriatric Hospital ▶ Education (highest grade completed) ▶ Smoking (No/Yes), if yes-how many cigarettes each day? How many years? ▶ Drinking (No/Yes), if yes-how much alcohol each day? How many years? ▶ When dementia was diagnosed

DBHDS Facility Name: *Piedmont Geriatric Hospital*

Telephone Number: 434-767-4401 **Fax**: 434-767-4404

Patient Name (Last, First, MI):	
DOB:	**SS# (optional)**

Extent or nature of use/disclosure is limited to: (Check √ or list all that apply)

☐ Discharge Summary	☐ History & Physical	☐ Social Work Assessment
☐ Psychiatric Evaluation	☐ Progress Notes	☐ Physician Orders
☐ Lab Work	☐ Consultations	☐ Treatment Plan
☐ HIV/AIDS Information	☐ Substance Abuse Information	☐ Psychological Evaluation

☒ Other: Medications, Functional scores, sex, marital status, age, race/ethnicity, length of stay, number of hospitalizations at PGH, education, information regarding smoking/drinking, when dementia was diagnosed

Specified purpose or need for use/disclosure is: ☐ Diagnosis/Treatment ☐ Discharge Planning ☒ Other, Specify Research project for a pharmacy graduate student to acquire a doctorate degree.

Permission is hereby given to: Facility Name & Name of Responsible Person e.g. ("Facility director or his authorized designee")	Piedmont Geriatric Hospital 5001 East Patrick Henry Highway Burkeville, VA 23922	
☒ **To disclose information to** **OR** ☐ **To exchange information with:** Name, or other specific identification and organization Street Address, City, State, Zip	Sheetal Dharia /Patricia Slattum, PharmD, PhD/ VCU School of Pharmacy Department of Pharmacotherapy and Outcome Science 410 North 12th Street / P. O. Box 980581 Richmond, VA 23298-0581	
Phone/Fax #	Phone: (804)828-6355	Fax: (804)828-1815
I also authorize the recipient to use the information received pursuant to this authorization.		

As the person signing this authorization, I acknowledge that I am giving my permission to the above-named person/class of persons to disclose and use protected health information. I further acknowledge that:

- I may refuse to sign this authorization.
- DBHDS/ Piedmont Geriatric Hospital cannot condition the provision of treatment to me on my signing of this authorization.
- The original or a copy of this authorization shall be included with my original records.
- I have the right to revoke this authorization at any time, except to the extent that action has been taken in reliance on it, by delivering the revocation in writing to the provider who is in possession of my health care records.
- There is a potential for any information disclosed pursuant to this authorization to be subject to re-disclosure by the recipient and, therefore, no longer protected by the provisions of the HIPAA Privacy Rule. If this information is being disclosed from records protected by the Federal substance abuse confidentiality rules (42 CFR part 2), the Federal rules prohibit the recipient from making any further disclosure of this information unless further disclosure is expressly permitted by your written authorization or as otherwise permitted by 42 CFR part 2. A general authorization for the release of medical or other information is NOT sufficient for this purpose. The Federal rules restrict any use of the information to criminally investigate or prosecute any alcohol or drug abuse patient.

If not previously revoked, this authorization will expire in:	☐ 90 Days	☐ One Year	☒ Upon project completion
The information may be disclosed effective:	☒ Immediately	☐ (specify date)	
This authorization ☒ does ☐ does not extend to information placed in my record after the date I signed this form.			

Signature of Individual (adult) or Legally Authorized Representative	**Relationship**	**Date Signed**
Signature of Minor (if required by law)		**Date Signed**
Witness (optional)		**Date Signed**

Appendix D: PGH Collection Form

	Subject Number:
Subject Collection Form	

Age	

Sex: M=0; F=1	

Marital Status	
Married=1 Single=2 Widowed=3 Divorced=4 Separated=5 Unknown=9	

Smoker	Yes	No	Previous
How long (years)?			
How Many Cigarettes/Day?			
Alcohol			
How many drinks per day?			
How long (years)?			

Highest Grade Achieved (Check 1)	< K-5	K-5	6-8
	9-12	> 12+	Other:

Date of Diagnosis	

Ethnicity/Race: White=1; Black=2; Hispanic=3; Asian/Pacific Islander=4; American Indian=5; Unknown=9	

Residence (prior to admission): Home (No Assistance)=1; Home(w/Assistance)=2; ALF=3; SNF=4; Unknown=9	

Length of Stay	

# of Admissions	

Alzheimer's Treatment: Aricept=1; Exelon=2; Razadyne=3; Namenda=4 Unknown=9	Yes ___ No ___ Previous ___	Dose per day:
Admission conditions: Absent=0; Present=1; Unknown=9		

HTN		Constipation		Seizures	
Bradycardia		Abdominal Cramps		Loss of Coordination	

Tachycardia		Vomiting		Confusion/ Delirium	
Arrhythmias		Urinary Incontinence		Depression	
Other CV		Nausea		Agitation	
Asthma		Loss of Appetite		TBI	
Pneumonia		Diarrhea		Parkinson's Disease	
COPD		Dry Mouth		Clots (Any)	
Cancer		High Cholesterol		Other:	
Wear Eyeglasses		Diabetes			
Use Hearing Aids		Thyroid Problems			

	FIMS	**Cognitve Problems**	**Behavioral Problems**	**ADS Score**
Date	Score	Yes=1; No=2	Yes=1; No=2	

Vita

Sheetal Prabodh Dharia was born on February 22, 1981, in Dunedin, Florida, and is an American citizen. She graduated from the International Baccalaureate program at Palm Harbor University High School, Palm Harbor, Florida in 1999. She received her Bachelor's of Science in Biology with a minor in General Business from the University of South Florida, Tampa, Florida in 2002 and subsequently worked for a biotechnology company, Digene Corporation, in Gaithersburg, Maryland for two years. Additionally she worked for CVS pharmacy for five years as a pharmacy intern. She received a Doctor of Pharmacy degree and a Certificate in Aging Studies from Virginia Commonwealth University in May of 2010.