2006

Length of Hospital Stay, Delirium and Discharge Status Outcomes Associated With Anticholinergic Drug Use in Elderly Hospitalized Dementia Patients

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LENGTH OF HOSPITAL STAY, DELIRIUM AND DISCHARGE STATUS OUTCOMES ASSOCIATED WITH ANTICHOLINERGIC DRUG USE IN ELDERLY HOSPITALIZED DEMENTIA PATIENTS

A Thesis submitted in partial fulfillment of the requirements for the degree of Master of Science at Virginia Commonwealth University.

by

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May 2006

Acknowledgement

I would like to thank all of my friends and loved ones for putting up with me during these past four years, I know it couldn't have been easy. I would like to especially thank John for all you have put up with and endured these past four years living with me. I couldn't have done it with all of their love and support backing me up. I would also like to give a special thanks to Dr. Slattum for always having the confidence in me when I was lacking it.

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List of Abbreviations

Anticholinergic ..... ACh

Activities of Daily Living ..... ADL

Alzheimer's Disease ..... AD

Alzheimer's Disease Assessment Scale-cognitive subscale ..... ADAS-cog

Antipsychotics. ..... AP

Blood Brain Barrier ..... BBB

Confusion Assessment Method ..... CAM

Cholinesterase Inhibitor ..... ChEi

Diagnostic & Statistical Manual of Mental Disorders-3rd ed. ..... DSM-III

Length of Stay ..... LOS

Long Term Care ..... LTC

Mini Mental State Examination ..... MMSE

Modified Clinician-rated Anticholinergic scale ..... mCr-ACh

Overactive Bladder ..... OAB

Serum Anticholinergic Activity ..... SAA

Tricyclic Antidepressants ..... TCA

Abstract

LENGTH OF HOSPITAL STAY, DELIRIUM AND DISCHARGE STATUS OUTCOMES ASSOCIATED WITH ANTICHOLINERGIC DRUG USE IN ELDERLY HOSPITALIZED DEMENTIA PATIENTS

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A Thesis submitted in partial fulfillment of the requirements for the degree of Master of Science with a concentration in Pharmacotherapy at Virginia Commonwealth University.

Virginia Commonwealth University, 2006

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Problem: There are a significant proportion of patients taking acetylcholinesterase inhibitors (ChEi) for cognitive dysfunction also taking medications with anticholinergic (ACh) properties that may counteract their effects. As the number of ACh medications, burden, increases so does the likelihood of an adverse outcome.

Background: ACh medications are frequently used in the elderly population (Carnahan 2004) even those with dementia or AD (Roe et al., 2002; Giron et al., 2001; Altavela 2003; Gill et al., 2005; Kogut et al., 2005).

Methods: Hospitalized patients $\geq$ 65 years of age with dementia (AD, other dementias, or with inferred dementia based on ChEi or NMDA antagonist medication use) were studied using UHC clinical database. This document was created in Microsoft Word 2000.

Results: Dementia patients on ChEi therapy were more likely to receive an ACh (chi-square 70.1, df=1, $p<.0001$) and had a significantly higher ACh burden ($p=.0017$) during hospitalization than those not on ChEi therapy.

Conclusion: A person's age and mental health status along with their current drug regimen, such as ChEi therapy, need to be closely and carefully considered before deciding to use unnecessary ACh drugs in this population which can have detrimental effects.

Chapter 1 Introduction

I. Introduction

Anticholinergic (ACh) medications are frequently used in the elderly population (Carnahan et al., 2004) even those with dementia or Alzheimer's Disease (AD) (Roe et al., 2002; Giron et al., 2001; Altavela, 2003; Gill et al., 2005; Kogut et al., 2005). Surveys of administrative claims data from state Medicaid plans (Slattum et al., 2001; Carnaham et al., 2004), found that 13.5% and 35.4% respectively of patients receiving cholinesterase inhibitors (ChEi) were also receiving ACh drugs with significant central activity during a 3-month period.

The use of ChEi therapy has been associated with an increased risk of receiving an ACh drug (Gill et al., 2005). Some patients may be prescribed an ACh medication or a medication with ACh side effects to treat the side effects of ChEi therapy (Hashimoto et al., 2000) such as those used to treat urinary incontinence (Roe et al., 2002; Gill et al., 2005). Even the use of incontinence medications to treat overactive bladder (OAB) in patients with AD, may have detrimental effects on mental status and behavior (Jewart 2005). Other drugs such as tricyclic antidepressants (TCA), antipsychotics (AP), antispasmodics, antiparkinsons (benzotropine, trihexyphenidyl), antiarrhythmic (disopyramide) and older-generation antihistamines (diphenhydramine,

dimenhydrinate, chlorpheniramine) with known ACh activity are also frequently used in AD patients. Most ACh medication use can be deemed as an inappropriate medication for use in the elderly population (Agostini et al., 2001; Sloane et al., 2002; Fick et al., 2003; Carnahan et al., 2004).

A number of studies have reported on the adverse effects associated with ACh drugs in general elderly populations. A few studies have found elderly to be at risk of cognitive impairment even at low serum ACh levels (Mulsant et al., 2003). Impairment of self-care capacity and cognition have been found to be associated with high serum ACh levels in dementia nursing home patients (Rovner et al 1988). AD patients are at risk of additional cognitive impairment from ACh drug therapy (Thienhaus et al., 1990).

The use of ACh medications or medications with ACh properties in community-dwelling elderly without dementia has been associated with lower cognitive performance (Lechevallier-Michel et al., 2004; Ancelin 2006). AD patients have shown clinically significant impairment of behavior and cognitive function (new learning and semantic knowledge) at lower doses of centrally acting ACh medications, such as scopolamine, compared to healthy, age-matched controls (Sunderland et al., 1987, 1988).

ACh load or burden is when there is more than one ACh drug or drug with ACh properties co-administered. There are numerous studies which have shown ACh burden to be a strong predictor of cognitive impairment (Golinger et al., 1987; Rovner et al., 1988; Mach et al.,1995; Mussi et al., 1999; Mulsant et al., 2003; Jeward et al., 2005; Chew et al., 2005) and may be associated with excess disability in nursing home patients (Rovner et al., 1988; Thienhaus et al., 1990). Tollefson et al., (1991), demonstrated that reducing ACh

load or burden can cause significant changes in short term memory, delirium, and behavior. Even low ACh drug levels can cause mild but measurable cognitive impairment in elderly patients (Miller et al., 1988; Sands et al 1997).

Nishiyama et al., (1998), found a strong relationship between long-term exposure to ACh medications and cognitive deficits with older Parkinson's disease patients. There was also a significant association of chronic use of ACh medications (ie. 2 or more years) with increased AD-type pathology in the frontal cortex, even though patients in the study were not sufficiently symptomatic to warrant a diagnosis of dementia clinically (Perry et al., 2003). A study by Lu and Tune found that chronic exposure of ACh therapy may be associated with either detrimental effects on concomitant ChEi therapy or adverse effects on the clinical course of AD (Lu and Tune 2003). In their study, AD patients taking ChEi therapy and at least one ACh medication had similar decline in MMSE scores over two years as AD patients who were not receiving ChEi therapy.

In hospital settings ACh medication exposure in older hospitalized patients has been associated with an increased risk of cognitive decline, behavioral disturbances and urinary catheter placement (Agostini et al., 2001; Han et al., 2001; Mulsant et al., 2004). A dose-response relationship has been demonstrated with diphenhydramine and adverse outcomes such as a significantly longer length of hospital stay and altered sleep-wake cycle (Agostini et al., 2001). Han et al., (2001), showed that ACh exposure, independent of initial severity of delirium or presence of delirium or other comorbid conditions, is associated with the severity of delirium symptoms in hospitalized elderly patients with diagnosed delirium.

The prevalence of delirium in older hospitalized patients is 10-25% and has significant human and economic burdens such as increased morbidity, a mortality of up to 40%, significantly increased hospital lengths of stay, institutionalization, and functional disability (Thomas et al., 1988; Francis et al., 1990, 1992; Levkoff et al., 1992; Inouye et al., 1993; Murray et al., 1993; Rockwood 1993). According to Francis et al., (1990), approximately 40% of delirium cases in hospitalized elderly patients can be attributed to medications.

II. Study Objectives

The specific aims of this study are:

- To determine the prevalence of ACh use in hospitalized elderly patients with dementia.
- To determine the prevalence of ACh use in hospitalized elderly patients with dementia on ChEi.
- To compare the prevalence of ACh use between hospitalized elderly patients with dementia on and not on ChEi therapy.
- To compare ACh burden between hospitalized elderly patients with dementia on and not on ChEi therapy.
- To characterize prescribing patterns of ACh medications in the hospitalized elderly, particularly those with dementia with or without ChEi therapy

- To compare the prescribing patterns of urinary antispasmodics, GI antispasmodics, and ACh antispychotics between hospitalized elderly patients with dementia on and not on ChEi therapy.
- To evaluate and compare the impact of ACh medication use in hospitalized dementia patients on length of hospital stay, discharge status, and having delirium while in the hospital.
- To evaluate and compare the impact of ACh burden in hospitalized dementia patients on length of hospital stay (LOS), discharge status, and having delirium while in the hospital.

III. Purpose and Significance

A. Purpose

The mainstay of AD treatment is through enhancing cholinergic neurotransmission with ChEi. Cholinesterase inhibitor therapy is associated with significant cost for AD patients. Giving other medications that block or counteract the potential benefits of this therapy make those costs an unnecessary burden on the family and the health care system as a whole.

The hypothesis guiding this research is that a significant proportion of patients taking ChEi for cognitive dysfunction are taking medications with ACh properties that may counteract their effects. As the number of ACh medications or ACh burden increases, so does the likelihood of an adverse outcome.

B. Significance

No studies have reported on the ACh effects in hospitalized dementia patients. No studies have examined whether the use of ChEi therapy in hospitalized dementia patients taking ACh medication will have any effect on the adverse events associated with the use of ACh medications. To date, there has been one study conducted in one hospital which evaluated the use of one ACh drug, diphenhydramine, in hospitalized elderly patients. This study will look at a clinical database with data on the use of numerous ACh medications from 42 academic health centers from across the country. The descriptive data obtained from this study will provide valuable information on the prevalence of concomitant use of ACh and ChEi therapies. This study will provide information on the adverse events associated with ACh use in dementia patients. It will also attempt to provide some insight on the differences of ACh prescribing patterns between dementia patients taking and not taking ChEi therapy.

Chapter 2 Literature Review

I. Alzheimer's Disease

A Medline/Pubmed search (time frame: up to January 2006) was performed to find articles on the course, pathology, and prevalence of AD, the role of cholinesterase and acetylcholine in AD, and the treatment of AD. Search terms used were: Alzheimer's disease, acetylcholine and Alzheimer's disease, cholinesterase and Alzheimer's disease, dementia, cholinergic receptor, muscarinic receptor, Alzheimer's disease treatment, and cholinesterase inhibitors and Alzheimer's disease.

AD is a progressive neurodegenerative disorder and eventually leads to death. It is the most common cause of dementia. A diagnosis of AD is not affirmative until death, upon autopsy. Prevalence studies suggested that in 2000, the number of persons with Alzheimer's disease in the United States was 4.5 million (Herbert et al., 2003). The percentage of persons with Alzheimer's disease increases by a factor of two with approximately every five years of age, meaning that 1 percent of 60-year-olds and about 30 percent of 85-year-olds have the disease (Jorm 1991). Without advances in therapy, the number of symptomatic cases in the United States is predicted to rise to 13.2 million by 2050 (Herbert et al., 2003). The cost of caring for patients with Alzheimer's disease is

extraordinary, with annual expenditures totaling $83.9 billion (in 1996 U.S. dollars) (Wimo and Winbald 2001).

There are three consistent neuropathological hallmarks in the pathology of AD: amyloid-rich senile plaques, neurofibrillary tangles, and neuronal degeneration. There are many hypotheses on the pathology of AD and what causes these hallmarks. One hypothesis is that the symptoms of AD result from the accumulation of beta-amyloid peptide. Other hypotheses associate AD pathology with the hyperphosphorylation of Tau protein, heavy metals, vascular factors, viral infections, and the loss of cholinergic neurons.

A. The cholinergic hypothesis

The cholinergic hypothesis correlates the loss of acetylcholine activity, due to death of neurons, with the severity of AD (Bartus et al., 1982). Compared to individuals without AD, patients with AD demonstrate significant reductions in cholinergic activity in areas of the brain (cortical and subcortical) important in the processes of memory and learning. The changes in cholinergic activity are due to reductions in choline acetyltransferase activity and number of cholinergic neurons in late AD, and selective loss of nicotinic receptor subtypes in the hippocampus and cortex (Bartus et al., 1982; Whitehouse et al., 1982; Guan et al., 2000).

These changes in the central cholinergic nervous system, both age- and disease-related, contribute to the functional decline, memory impairment, behavioral disturbances, and worsening quality of life seen in AD. It has been demonstrated by numerous studies

that the extent of cholinergic loss in AD is correlated with the severity of cognitive dysfunction and disease duration, as well as with the density of senile plaques of beta-amyloid protein and intracellular neurofibrillary tangles (Perry et al 1978; Bierer et al., 1995; Bowen et al 1982; Cummings and Cotman 1995; Everitt and Robbins 1997).

B. Treatment of AD

Because of the functional outcomes of AD (functional decline, memory impairment, behavioral disturbances, and overall worsening quality of life) and the fact that there has been death of neurons, leads us to how AD is treated. In AD treatment only the the symptoms are treated and not the disease itself.

The first treatment approach and currently the mainstay in mild to moderate AD is the enhancement of cholinergic transmission with ChEi. ChEi enhances cholinergic neurotransmission through inhibition of cholinesterase, the enzyme responsible for hydrolyzing acetylcholine, in the central nervous system and therefore allowing acetylcholine to remain in the synaptic cleft longer (Hogan and Patterson, 2002). Maximizing cholinergic function may help patients maintain their ability to perform activities of daily living (ADLs), temporarily slow cognitive decline/functional deterioration, reduce emergence of behavioral disturbances, reduce caregiver burden and defer placement in long term care (LTC) facilities (Cummings, 2004). Studies of ChEi therapy show that there is a four to seven point improvement on the AD Assessment Scale-cognitive proportion (ADAS-cog), a psychometric test, commonly used to establish efficacy with respect to cognitive function.

Maximizing the cholinergic system, also causes the common side effects of nausea, diarrhea, and urinary incontinence through increasing activity at peripheral muscarinic receptors. The actual incidence of urinary incontinence and how often ChEi therapy worsens it are unknown.

A newer approach in the treatment of AD is memantine (Nemenda ®), a N-methyl-D-aspartate antagonist approved for treatment of moderate to severe AD. Its benefits are either through interfering with the glutamatergic excitotoxicity caused by beta-amyloid peptide or its effects of symptomatic improvement on the hippocampal neurons (Parsons et al., 1999). In clinical trials there were no clinically relevant differences between moderate to severe AD patients in the memantine and placebo groups in terms of adverse events, laboratory findings, electrocardiographic studies, or vital signs. When memantine was administered to patients with moderate-to-severe Alzheimer's disease who were receiving stable doses of a ChEi, cognitive improvement was seen as a reduced decline in ADLs and a reduced frequency of new behavioral symptoms as compared with those receiving placebo (Tariot et al., 2004). The magnitude of the improvements in patients in these trials is modest, with improvement or temporary stabilization observed in daily function or behavior.

II. Anticholinergics

A Medline/Pubmed search (time frame: upto January 2006) was performed to find articles on ACh and their effects on the geriatric population ($\geq$ 65), both demented and non-demented, and their use in geriatrics. Search terms used were: anticholinergic,

anticholinergic and Alzheimer's disease, anticholinergic and cognitive function, anticholinergic and dementia, anticholinergic and memory, anticholinergic and elderly, anticholinergic and geriatric, anticholinergic and older persons, anticholinergic and side effects, anticholinergic and urinary incontinence, treatment of overactive bladder, and prevalence of anticholinergic and elderly.

ACh bind to muscarinic receptors to block acetylcholine actions and hence decrease cholinergic neurotransmission. ACh medications are often used in the treatment of movement disorders like Parkinson's Disease (benztropine, trihexyphenidyl), urinary incontinence (tolterodine, oxybutynin, and the newer agents), dizziness (meclizine), and insomnia (diphenhydramine). The common side effects of ACh are dry mouth, disorientation, confusion, delirium, memory impairment, sedation, blurred vision, changes in heart rate (bradycardia or tachycardia), urinary retention, and constipation.

A. Muscarinic receptors

There are two types of cholinergic (ACh) receptor systems: muscarinic and nicotinic. There are at least five subtypes of muscarinic receptors (M_1, M_2, M_3, M_4, and M_5) which can be found distributed throughout the brain and (M_1, M_2, M_3, and M_4) in different areas of the body. Areas of the body where the different receptor subtypes can be found are listed in Table 1 on the following page.

Table 1. Locations of muscarinic receptor subtypes

Receptor subtype	Location
M_1	brain (cerebral cortex, hippocampus, & neostriatum), bladder, salivary glands, sympathetic ganglia
M_2	brain (throughout), bladder, eyes, heart, smooth muscle
M_3	brain, eyes, smooth muscle, salivary gland, bladder
M_4	brain (neostriatum, cortex, hippocampus), bladder, salivary glands
M_5	brain (hippocampus & projection neurons of substantia nigra, pars compacta, & ventral tegmental area), eyes (ciliary muscles)

All muscarinic receptor subtypes (M_1-M_4) are present in various regions of the human brain. Of the receptor subtypes, M_1 is the most abundant in the cerebral cortex and hippocampus, M_2 are located throughout the brain, and M_3 are located in low levels throughout the brain. The muscarinic receptors of the brain are involved in several processes including memory, learning, control of movement, nociception, and regulation of circadian rhythm.

The cholinergic system exerts a major influence on the cognitive process, in particular memory via M_1 cholinergic receptors as demonstrated through studies using genetically modified (knockout) mice. Inhibition of the M_1 subtype in the brain is known to disrupt cognitive functions such as learning and memory (Kay and Granville 2005). Recent evidence suggests a role for M_2 (Teaktong et al., 2005) receptors in mediating cognitive function. Similar studies with knockout mice lacking M_2 receptors show significant deficits in behavioral tasks requiring working memory and dysregulation of cholinergic function in the hippocampus, which are associated with cognitive deficits (Lazaris et al., 2003). Other genetic studies have implicated a role for striatal M_4 autoreceptors in the regulation of acetylcholine levels (Zhang W et al., 2002).

Approximately two-thirds of the muscarinic receptors of the bladder are M_2 and one-third M_3. Both M_2 and M_3 muscarinic receptors facilitate contraction of the bladder, but the M_3 subtype is principally responsible for detrusor muscle contraction.

B. ACh and their use in urinary incontinence

New onset or worsening incontinence is commonly seen as part of the natural history of dementia (Skelly and Flint 1995) and are highly prevalent and likely to occur simultaneously in the elderly. Urinary incontinence occurs in approximately 33% of women and 15-20% of men over the age of 65, 50% of frail elderly or those over the age of 85 who have multiple comorbidities and at least 60-80% of residents of nursing homes or skilled facilities receiving around the clock care (Jewart et al., 2005). Urinary incontinence is not only common in frail older adults, but has been associated with significant morbidity, specifically premature nursing home placement (Thakar et al., 2000).

ACh agents such as oxybutynin, tolterodine, trospium, darifenacin, and solifenacin (Table 2) are frequently used to treat overactive bladder in the elderly population and in particular those with AD or Parkinson's disease (PD).

Table 2. ACh agents available for the treatment of OAB

Drug	Formulation	Dosing	chemical structure	selectivity
Tolterodine (Detrol)	IR ER	1,2 mg BID 2,4mg QD	nonlipophilic, tertiary amine	nonselective
Oxybutynin (Ditropan)	IR ER skin patch	5mg BTID 5, 10, 15, 20mg QD 3.4mg/d every 3-4days	lipophilic, tertiary amine	M_3, M_1 >>M_2
Trospium (Sanctura)	IR	20mg BID (at least one hr before food)	quaternary amine	nonselective
Darifenacin (Enablex)	CR	7.5, 15mg QD	tertiary amine	M_3
Solifenacin (Vesicare)	CR	5,10mg QD	tertiary amine	M_3

IR: immediate release; ER: extended release; CR: controlled release; QD: once daily; BID: twice daily; BTID: 2-3 times daily

ACh agents currently used in the treatment of OAB have the potential to bind to muscarinic receptors throughout the body, thereby mediating a variety of related adverse events. There is growing evidence from different sources suggesting that treatment of OAB with nonselective muscarinic antagonists may result in memory dysfunction (Tsao and Heilman, 2003; Womack and Heilman, 2003), confusion and disorientation (Edwards and O'Connor 2002) in the elderly population.

There are other factors that can affect a drugs capability to exert its effects on the CNS by crossing the blood brain barrier (BBB). Factors that favor a medication's passive penetration of the BBB include lipophilicity, a neutral charge, and a smaller, less bulky molecular size. Trospium is the only quaternary amine used in the treatment of OAB. The quaternary amine gives the trospium molecule a positive charge making it highly polar and decreased lipophilicity and therefore is less likely to cross the BBB than the tertiary amines. Its nonspecific effects are mainly seen in the periphery.

Even though there are urinary incontinence medications that are receptor specific or have a permanent charge to reduce its crossing of the BBB, there are still a number of conditions that can increase the BBB permeability and therefore allowing drugs to cross the blood brain barrier that would not have normally. These include being elderly ($\geq$ 65), use of certain medications, comorbid diseases and stress (Pakulski et al., 2000; Star et al., 2003; Abdel-Rahman et al., 2004). The integrity of the BBB in those 65 years old and older is unknown. Quaternary amines have been shown to cross an intact BBB in animals exposed to stress (Abdel-Rahman et al., 2004). There are also many comorbid conditions that are common in older people that may make them more susceptible to cognitive impairment and exaggerate the ACh drug effects on cognitive function (Doraiswamy et al., 2002). Such conditions are type II diabetes mellitus, coronary artery bypass graft surgery, cerebrovascular disease, Parkinson's disease, and AD and related dementias. In other words, all ACh medications, regardless of their physiochemical properties, should be considered to have the potential to cross the BBB.

C. Concomitant use of ACh and ChEi

There have been numerous studies that have looked at the prevalence of the concomitant use of ACh and ChEi drugs. These studies are summarized in Table 3. Studies by Carnahan and Roe found that approximately 35.4% of those on ChEi therapy were also receiving at least one ACh, defined as ACh agents with clinically relevant ACh properties from the Beer's criteria (Carnahan et al., 2004; Roe et al., 2002). Surveys of administrative claims data from Medicaid plans found that 13.5-35% of patients receiving

ChEi therapy were also receiving ACh drugs with significant central activity (Slattum et al., 2001; Carnahan et al., 2004). Carnahan et al., (2004), was from January 1997 to Febuary 2000. The use of ChEi therapy has been associated with an increased risk of receiving an ACh drug to manage urinary incontinence (Gill et al., 2005).

Table 3. Published studies of the prevalence of concurrent ChEi & ACh

Authors, yr	Patient population	Study Design	Conclusion/findings
Roe CM, Anderson MJ, Spivack B. 2002	n=836 (418 on donepezil; 418 not on donepezil therapy) community-based adults (≥65)	each member from ChEi group was matched with a member from the comparison group used 3-12 months of pharmacy claims data	• older adults w/probable dementia were more likely to use ACh. • In ChEi group, those receiving ACh: 33% used ≥1 ACh med; • community-based, commercially insured, older adults w/probable dementia are more likely to take ACh (TCAs,, antipsychotics, UI drugs) than matched controls.
Carnham RM, Lund BC, et al., 2004	n=557 Iowa medicaid beneficiaries (≥50)	pharmacy claim for ChEi & ACh over a 180d period, counted #ACh received and timing (before or after ChEi initiation)	• 35% of pts receiving ChEi also received ≥1 ACh; o those receiving ACh: nearly 75% were considered as inappropriate for use in elderly ▪ of which 22% were deemed inappropriate under any circumstance. • ACh prescibing upon ChEi therapy inception: cimetidine, ranitidine, atropine, dicyclomine, hyoscyamine, oxybutynin, & tolterodine
Gill SS, Mamdani M, et al., 2005	n= 44884 study of older adults; (n=20491) w/ dementia who received ChEi therapy (n=24393) who didn't	-used administrative health care databases of Ontario, Canada -use of oxybutynin, tolterodine, or flavoxate initiation of oxybutynin, tolterodine, or flavoxate, for treatment of urinary incontinence after ChEi therapy is started	• There was a significant increase in receiving an ACh after initiation of ChEi therapy; risk was same among the LTC and community-dwelling settings • use of ChEi was associated with an increased risk of receiving an ACh drug to manage urinary incontinence
Kogut SJ, El-Maouche D, Abughosh SM. 2005	n=1183 (≥45) residing in the community or LTC facility dispensed a ChEi	Use of developed list of drugs that can impair cognition through review of similar lists used by other researches	• approximately 60% of patients taking ChEi also received a drug that can impair cognition

There are many reasons cited in the literature as to why ACh and ChEi should not be used together. The American Psychiatric Association and the American Academy of Neurology both have guidelines that reinforce the warning of the high risk of adverse effects of ACh drugs given to patients with dementia.

Chronic exposure to ACh medications can adversely affect the course of AD (Lu and Tune 2003). In a two year retrospective study in 69 patients diagnosed with probable AD and receiving donepezil, patients were divided into two groups based on the number of ACh medications they were concomitantly taking. Sixteen subjects received at least one ACh medication and 53 were not taking any ACh drugs concomitantly. Patients took an annual Mini Mental State Examination (MMSE) and had blood drawn for the serum anticholinergic activity (SAA) radioreceptor assay. They found that those patients that were receiving ACh drugs showed a significantly greater decline, an average decline of 7 points over 2 years, in MMSE scores than those who were not taking ACh drugs, average decline of 3 points over 2 years. Those that were taking ACh concomitantly experienced similar declines in their MMSE scores as patients who do not take ChEi therapy (average decline of 3.5 points per year) (Burns et al., 1991). The findings suggest that concomitant treatment with ACh drugs may be associated with significant deleterious effects on ChEi therapy or that chronic exposure to ACh may have adverse effects on the clinical course of AD.

Studies by Sunderland et al and Agnoli et al., have shown that the addition of medications with ACh properties may diminish any potential benefits from ChEi and possibly exacerbate cognitive decline in AD patients (Sunderland et al., 1987, 1988;

Agnoli et al., 1983). AD patients are at risk of additional impairment from ACh drug therapy (Thienhaus et al., 1990). In an observational study in geropsychiatric inpatients, ten with probable AD and 18 without significant impairment, participants were subject to a battery of cognitive tests and had their SAA measured. Non-demented subjects were significantly less vulnerable to the cognitive effects of ACh drugs than were the demented patients. The implication being that ACh drugs may be associated with excess disability in geriatric inpatients. There have also been case reports of delirium with oxybutynin and tolterodine in patients that were also concomitantly taking ChEi therapy (Edwards et al., 2002)

D. ACh and Delirium

ACh medications are a well-known cause of delirium most likely due to a direct reduction in central cholinergic activity. Numerous challenge studies have found impairments in various aspects of cognitive function after administering standard therapeutic doses of ACh medications to normal healthy adults (Mulsant et al., 2003; Rovner et al 1988; Katz et al., 1998; Lechevallier-Michel et al., 2004; Ancelin 2006).

The results of the Sunderland et al., study suggest that dementia may modify the ACh-delirium relationship. Their study, patients with dementia showed significant cognitive decline at doses of ACh medications at which their non-demented controls did not (Sunderland et al., 1987).

Cholinergic antagonistic binding at these muscarinic receptors can further impact dementia and cognitive deficits in patients with dementia of Lewy bodies (DLB), which

accounts for 15-25% of dementia in the elderly (Teaktong et al., 2005), and those with Alzheimer's disease (AD). Therefore current data suggests that cognitive impairment, in particular memory dysfunction, could result from antagonism of M_1 and to some extent M_2 and M_4 receptors in the CNS. Thus, older patients with existing cognitive impairment, especially those with early-stage dementia, age-associated memory impairment, or mild cognitive impairment may be especially vulnerable to these cognitive side effects.

Numerous studies have noted an association between medications with ACh properties and delirium. Table 4 summarizes studies on ACh drug use and their association with delirium. Even though this syndrome has long been recognized, the full extent of its nature is not yet fully understood. The ACh effects of many drugs and their metabolites are unknown and since most elderly patients take a number of medications, it is difficult to discern what their ACh burden is, thus there needs to be a method for measuring or assessing one's ACh burden.

Table 4. Published studies: ACh and delirium

Authors, yr	Patient population	Definition of Ach drug or burden & delirium meaurement	Conclusion/Findings
Tune LE, et al., 1981	n=29 cardiac surgery pts (29-75 yo)	10 delirious pts 19 control pts	delirium was significantly associated with SAA. higher SAA was associated with lower MMSE
Golinger RC, Peet T, Tune LE. 1987	n=16 surgical ICU pts. (29-76 yo)	Plasma AA & drug-risk number	Plasma AA was signifiicantly higher in the delirious pts (ave age=60) than in the pts w/o delirium (ave age=57).
Francis et al., 1990	n=229 community-dwelling elders admitted to medical ward (≥ 70)	MMSE, DSM-III and noted if pt had taken an ACh	ACh drug use was not associated with delirium.
Schor et al., 1992	n=291 general and medical ward pts (≥ 65)	DSM-III and counted number of doses received	Delirium not significantly associated with ACh drug use

(Table 4 continued from pg 19)

Authors, yr	Patient population	Definition of Ach drug or burden & delirium meaurement	Conclusion/Findings
Tune LE, et al., 1993	n=25 surgical ICU pts (29-74 yo)	SAA & DSM-III	Significant relationship between SAA and delirium.
Marcantonio et al., 1994	n=91 surgical pts	MMSE, CAM, and counted number of doses received	Delirium not significantly associated with ACh drug use
Mach JR, Dysken MW, et al., 1995	n=12, male delirious & non-delirious pts (≥ 60) case-control study & with-in subjects repeated-measures in recovered delirious pts	SAA	mean SAA was significantly elevated in delirious group vs non-delirious group
Flacker JM, et al., 1998	n=67 medical ward pts ≥ 75 yo	20 delirious patients vs 47 non-delirious patients	SAA was associated with delirium in a multivariate analysis
Flacker JM, Lipsitz LA. 1999	n=22 NH residents	8 delirious pts 14 non-delirious pts	SAA appears to be elevated during illness, and declines following recovery from illness and not associated with delirium.
Mussi C, Ferrari R, et al., 1999	n=61; elderly pts (≥ 66 yo) admitted to hospital	divided into 2 groups based on presence (n=12) or absence (n=49) of delirium	high levels of SAA were significantly correlated with delirium

yo= years of age; pts= patients; AA= ACh activity; BZ= benzodiazepines

III. Delirium and Adverse Outcomes

A Medline/Pubmed search (time frame: upto January 2006) was conducted to find articles on delirium and its effects on the geriatric population (≥ 65), and the frequency of delirium occurrence and adverse outcomes associated with developing delirium during hospitalization in the elderly. Search terms used were: delirium and geriatric, delirium and elderly, delirium and older persons, delirium and hospitalization, delirium and morbidity, and delirium and mortality.

Delirium is defined as an acute disorder of attention and cognition and occurs in 14-56% of hospitalized elderly patients (Rosin and Boyd 1966; Chisholm et al., 1982; Gillick et al., 1982; Levkoff et al., 1992; Inouye et al., 1993). Delirium has been associated with several adverse outcomes such as increased rates of morbidity, mortality and institutional placement, and with longer, costlier hospitalizations (Weddington 1982; Thomas et al., 1988; Rockwood 1990; Levkoff 1992). Mortality rates of 12-76% have been reported (Weddington 1982; Lagoe RJ 1986; Thomas et al., 1988).

In a prospective study by Francis et al.,, participants in the study were 70 years or older, admitted directly to the medical ward from the community and underwent evaluation within in 48 hours of admission. The evaluation included an interview, chart review, MMSE, an assessment of ADL, and Blessed's Dementia Rating Scale. Patients were followed up on six months after discharge by phone. Patients who developed delirium stayed an average of 12.1 days longer in the hospital than those who did not. They also were 8% more likely to die or 16% more likely to be institutionalized compared to those who did not develop delirium (Francis et al., 1990).

Medical comorbidity and predisposing, as well as precipitating, factors are important to consider in the management of delirium. Major risk factors for delirium include advanced age, cognitive impairment, and chronic medical illness (Williams et al., 1985; Foreman 1989; Francis et al., 1990; Schor et al., 1992).

Schor et al., calculated incidence of delirium and risk factors for delirium in elderly hospitalized patients. Patients in their study were 65 years or older admitted from either a rehabilitation center for the aged or the community. Diagnosis for delirium was based on

Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III). In the Schor et al., study nearly one third of the 325 patients who participated developed delirium. Patients who developed delirium had a mean length of stay of 18.8 days vs 13 days in those who did not develop delirium (Schor et al., 1992). Almost 50% had met the DSM-III criteria for delirium by day 3 and 91% by day 7 of their hospital stay. Admission risk factors found to be strongly predictive of delirium were age greater than 80, prior cognitive impairment, fracture on admission, and institutionalization prior to admission.

Levkoff et al., evaluated the occurrence and persistence of delirium in 325 elderly patients admitted to a teaching hospital from either the community or LTC facility. On admission approximately 11% met DSM-III criteria for delirium and of the remaining patients nearly one third developed new onset delirium during their hospitalization. Risk factors identified in this study for the development of delirium were preexisting cognitive impairment and advanced age. Increased risk of developing delirium was seen in those admitted from the community and not from institutions. They also found delirium to be associated with prolonged hospital stay and an increased risk of institutional placement among the community dwelling but not an increased risk of mortality (Levkoff et al 1992).

IV. Assessing ACh burden

ACh burden refers to the cumulative effect of taking multiple drugs with ACh activity. A Medline/Pubmed search (time frame: upto March 2006) was conducted to find all articles that used ACh burden as a predictor of delirium in elderly individuals to see

how ACh burden was calculated and defined. Search terms used were: anticholinergic burden, serum anticholinergic activity, anticholinergic activity, and anticholinergic effects.

There are four general methods for measuring ACh burden they are: measurement of total SAA resulting from drugs, metabolites, and patient physiology; ACh drug lists combined with clinical judgement; measurement of individual drug-related ACh activity; and measurement of individual muscarinic receptor affinity in vitro. Sometimes these methods are combined.

A. Serum Anticholinergic Activity

One commonly used method for measuring ACh burden is by measuring the SAA. SAA was first described by Tune and Coyle (1980) to quantify the ACh burden of drug exposure. The assay is performed by incubating a small amount of sample solution of an ACh in a phosphate buffer containing [^{3}H]quinuclidinyl benzilate (QNB), a potent muscarinic antagonist, and a suspension of rat striatal membranes, which are rich in muscarinic receptors. The ACh substances in the sample competitively inhibit the binding of the radioactively labeled QNB to the receptors to a degree determined by their concentrations and affinity for these receptors. In other words, it measures the binding affinity, ACh potency (the higher the binding affinity the greater the ACh potency) of ACh drugs and also of non-ACh drugs that exhibit ACh-like properties such as TCA. The binding affinity is usually measured in atropine equivalents so that comparisons may be made across different drugs. SAA has been used in many studies and has been found to be associated with mental status changes in a number of clinical settings and patient

populations. Table 5 summarizes all of the published studies reviewed on the relationship of SAA and cognition.

SAA was measured in postoperative cardiac patients from 29-75 years of age (Tune et al., 1981). Elevated levels were significantly associated with an increased risk of delirium and reductions in scores on the MMSE correlated with SAA levels ($p < .001$). Another study (Golinger et al., 1987) looked at surgical patients in the ICU ranging from 25-76 years of age and found that mean SAA was significantly greater in delirious patients than in nondelirious patients ($p < .05$).

Flacker et al., 1998, found an association between higher SAA levels with delirium in 67 medical inpatients over 75 years of age ($p = .006$). The patients SAA levels were put into quintiles, 1 being the lowest and 5 the highest levels. The prevalence of delirium increased steadily from 7.7% in the first quintile to 61.5% in the fifth quintile.
In another study by Flacker et al., 1999, SAA, MMSE, and the delirium symptom interview were measured in 22 nursing home residents during a febrile illness and then again at one-month follow-up. Those in the delirious group had higher Cognitive Performance Scale scores, indicating more impairment, than those that were not delirious ($p < .01$). SAA in this study was not significantly different between the groups at baseline or at follow-up.

In a study for risk factors for delirium in patients admitted to a geriatric medical ward, Mussi et al., 1999 found that elevated SAA levels were independently associated with the presence of delirium ($p < .004$) along with antipsychotic use ($p < .002$) and benzodiazepine use ($p < .005$).

Rovner et al., 1988, studied the relationship between SAA levels and self-care capacity in 22 demented nursing home patients. Those patients that had SAA levels above the median SAA displayed significantly greater impairment in self care than did patients below the median ($p = .03$).

Miller et al., 1988, evaluated cognitive function in relation to SAA in presurgical patients over the age of 59 and showed that even low SAA levels can significantly impair patient's performance on cognitive testing. Cerebrospinal fluid ACh activity was measured in nine patients who received spinal anesthesia and was found to be significantly correlated with SAA ($p<.05$).

Thienhaus et al., 1990, studied SAA effects in geropsychiatric inpatients with probable AD compared to patients without cognitive impairment. In the probable AD patients there was a significant increase in SAA with the implemented drug therapy and SAA was significantly associated with worsening on a number of cognitive measurement scales. This same finding was not found in the patients without cognitive impairment suggesting that demented patients may be more susceptible to the detrimental cognitive effects of ACh medications than nondemented patients.

Table 5. Published Studies: Relationship between SAA and cognition

Authors, yr	Patient Population	Study Design	Outcome Measure(s)	Conclusion/ Findings
Tune LE, et al., 1981	n=29 cardiac surgery pts (29-75 yo)	10 delirious pts 19 control pts	SAA	-delirium was significantly associated with SAA. -higher SAA was associated with lower MMSE
Mondimore FM et al., 1983	post-ECT pts (17-76 yo)	pts treated with atropine	SAA and MMSE	higher SAA levels associated with decrease in MMSE

(Table 5 continued from page 25)

Authors, yr	Patient Population	Study Design	Outcome Measure(s)	Conclusion/ Findings
Golinger RC, Peet T, Tune LE. 1987	n=16 surgical ICU pts (29-76 yo)	9 delirious pts 16 non-delirious pts	plasma ACh activity MMSE calculated drug-risk	plasma ACh significantly higher in the delirious pts than in the pts without delirium
Miller PS, Richardson JS, et al., 1988	n=36 presurgical elderly pts (≥59 yo)	Scopolamine (n=14) placebo (n=16)	SAA & CSF ACh levels; mental status battery test (RAVL).	low ACh drug levels can cause mild but measurable cognitive impairment in elderly pts.
Rovner BW, David A, et al., 1988	n=22 demented NH pts	All residents with cognitive impairment	MMSE; SAA	-SAA levels were related to cognition & capacity for self-care. -high ACh levels associated with greater impairment in self-care capacity than pts with low levels
Thienhaus, Allen, et al., 1989	n=28 geropsychiatric inpatients	probable AD (n=10) compared to pts without significant cognitive impairment (n=18)	MMSE, Digit Retention Span, word recognition, category retrieval, Self-rated Memory Scale (SRM); SAA	-non-demented subjects were significantly less vulnerable to cognitive effects of ACh than demented pts -cognitive performance decreased as ACh load increased
Tollefson GD, Montague-Couse J, Lancaster SP. 1991	n=34; NH residents ≥ 65yo receiving ≥1 ACh medicine	15 intervention pts 19 control pts	SAA; battery of Psychometric testing	reducing ACh load gave a lowered SAA and was significantly related to improved cognitive performance
Tune LE, et al., 1993	n=25 surgical ICU pts (29-74 yo)	9 delirious pts 16 control pts	SAA & DSM-III	Significant relationship between SAA and delirium.
Mach JR, Dysken MW, et al., 1995	n=12 ≥ 60 yo male delirious & non-delirious pts	11 delirious pts 11 control pts	SAA	Resolution of delirium was associated with decrease in SAA
Nebes RD, et al., 1997	n=36; geropsychiatric pts, mean age of 69	17 with undetectable SAA; 19 with detectable SAA	SAA	detectable SAA was associated with lower cognitive performance
Flacker JM, et al., 1998	n=67 medical ward pts (≥ 75)	20 delirious patients vs 47 non-delirious patients	SAA & Delirium symptom interview	SAA was associated with delirium in a multivariate analysis
Flacker JM, Lipsitz LA. 1999	n=22 NH residents	8 delirious pts 14 non-delirious pts	Cognitive performance scale (CPS); SAA	SAA appears to be elevated during illness, and declines following recovery from illness and not associated with delirium.
Mussi C, Ferrari R, et al., 1999	n=61; elderly pts (≥ 66 yo) admitted to hospital	divided into 2 groups based on presence (n=12) or absence (n=49) of delirium	CAM for presence of delirium; SAA	high levels of SAA were significantly correlated w/delirium,
Mulsant BH, Pollock BG, et al., 2003	n=201; community study based on age & sex (≥ 65)	21 pts with undetectable SAA 159 pts with low SAA 21 pts with high SAA	cognitive performance: MMSE; SAA	2 strongest predictors of cognitive imprt: MMSE & ACh load. Ach load was a very strong predictor in degree of cognitive impairment, even low SAA was associated with cognitive impairment.
Chew ML, Mulsant BH, et al., 2005	n=26; geropsychiatric inpts treated for behavioral disturbx assocd w/dementia	Baseline SAA	cognition: MMSE & severe impairment battery; SAA	in patients with moderate-severe dementia- higher SAA assocd with lower cognitive performance

pts: patients; yo: years of age; SAA= serum ACh activity; d/o=disorder

The advantage to this method is that it has been shown in numerous studies to be related to cognitive impairment or improvement. Limitations to this method of measuring ACh burden are that it is an invasive procedure which requires blood samples to be drawn. Also, it is not a commercially available test and it doesn't provide a basis on which to rank the contribution of ACh activity from individual drugs and therefore limits its use in clinical practice and research studies.

B. ACh drug lists combined with clinical judgment

There are several subjective and objective published developed lists (Flacker et al., 1998; Mintzer 2000; Tune 2001; Miller 2002; Roe et al., 2002; Mulsant et al., 2003; Mann et al., 2003; Defilippi 2003; Scheife et al., 2005) available that can be used in combination with clinical experiences, to rate the ACh activity of the drug in question. Table 6 summarizes all of the published lists.

The subjective assessment relies heavily on clinician knowledge of physical and cognitive impairments associated with ACh drugs. The objective approach makes use of physical or cognitive rating scales to quantify drug-related ACh effects, for example AIMS (the Abnormal Involuntary Movement Scale). Other types of published lists that have been developed are those based on clinican experience and objective measures. An example of this would be the Beer's criteria, which is a list of drugs which should be avoided in the elderly (Beers 1997; Fick et al 2003).

The advantage to using this method is that it can serve as an aid or a guide to help a clinician decide the degree of risk an ACh drug may pose for an individual. The limitations are that it depends on the clinician's perspective, knowledge, and experience. The list must be combined with clinical judgement and then applied to each practice setting. There is no standardized, comprehensive ACh drug list available. Even with the combination of clinical tools such as the MMSE, which is not sensitive enough to detect mild drug-induced cognitive changes produced by ACh drugs, other tools such as the AIMS test have not been validated to ensure accuracy in detecting physical changes due to ACh drug reduction or discontinuation.

Table 6. Drugs with Definite or Possible ACh effects

DEFINITE EFFECTS:	
Antispasmodics	GI: atropine, belladonna alkaloids, clinidium-chlordiazepoxide, dicyclomine, diphenoxylate, hyoscyamine, scopolamine urinary: oxybutynin, tolterodine muscle: carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, orphenadrine
Antidepressants	TCA (amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline)
Antipsychotics	olanzapine, perphenazine, promazine, thioridazine
Antiparkinsons	benztropine, trihexyphenidyl
Antihistamines	chlorpheniramine, cyproheptadine, dexchlorpheniramine, diphenhydramine, hydroxyzine, meclizine
Antiemetics	dimenhydrinate, prochlorperazine, promethazine, trimethobenzamide
Benzodiazepines	alprazolam, clorazepate, chlordiazepoxide, diazepam, flurazepam, oxazepam
Cardiovascular	disopyramide, procainamide
POSSIBLE EFFECTS:	
Antipsychotics	chlorpromazine, clozapine, fluphenazine, haloperidol, olanzapine, quietapine, risperidone, thiothixene, trazodone,
Antidepressants	SSRIs (escitalopram, citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)
Antidiarrheal	diphenoxylate
Cardiovascular	captopril, digoxin, dipyridamole, doxazosin
Miscellaneous	codeine, prednisolone, prednisone

Adapted from references: Flacker et al., 1998; Mintzer 2000; Tune 2001; Miller 2002; Roe et al., 2002; Fick et al., 2003; Mulsant et al., 2003; Mann et al., 2003; Defilippi 2003; Scheife et al., 2005

C. Measurement of individual drug-related ACh activity

This method also uses the radioreceptor assay but *in vitro* (use of a standard concentration of a drug instead of patient's serum) to identify the ACh activity of individual drugs (Tune et al., 1991, 1992, 1993, 1999, 2000). Many of these studies have looked at drugs that are commonly used in the elderly.

The advantage to using this method is that it allows for the direct comparison of ACh activity of different drugs using atropine equivalents. The higher the atropine equivalent the more likely the drug will express ACh properties. One drawback is it does not account for varying drug dosages, pharmacokinetics, or differences due to individual patient physiology. Another limitation is that standardized drug concentrations may not reflect the concentration achieved at physiological conditions, nor of metabolites or the effects of protein binding.

D. Measurement of individual muscarinic receptor affinity *in vitro*

This method focuses on the drug-receptor interaction through direct measurements of receptor affinity by comparing the competitive binding between a radiolabeled muscarinic-cholinergic agonist and a study drug with muscarinic ACh receptor.

It could be used clinically to compare the relative differences in muscarinic receptor affinity as an indicator of a drug's ACh activity. The limitations of this method are that a drug's ACh activity is relative to the drug concentration necessary to produce 50% binding inhibition of a radiolabeled cholinergic agonist. There is also very limited

published data of dissociation constants for many drugs, which limits the utility of this approach.

E. Combination

There has been some research done using a combination of the above methods to measure ACh burden, each combination different from the other. One attempt to bring clinical utility to SAA is through using it to validate an ACh scale that can be used in practice to assess ACh burden (Carnahan et al., 2002). Carnahan et al., modified the original ratings of the Clinician-rated ACh scale (Han et al., 2001) only if there was compelling evidence such as receptor binding studies or clinically documented ACh effects to warrant the change. They then used SAA to validate the modified version (mCr-ACh scale) to assess ACh burden. The mCr-ACh scale rates the ACh nature of each medication on a scale of 0-3; 0 has no known ACh properties, 1= potentially ACh as evidenced by receptor binding studies, 2 = ACh effects sometimes noted but usually from excessive doses, and 3 = markedly ACh. Scores of the individual drugs taken by study participants were summed to determine their ACh burden. They found significant correlation between SAA and the mCr-ACh scale but the scores only explained a small variance in the observed SAA among the study participants which could be due to some of the limitations of this method. A limitation to the mCr-ACh scale is that it does not allow for differences in dosages nor take into account the differences in subject pharmacokinetics. By lumping ACh drugs into general categories it assumes that they are equally ACh when in fact this is most likely not the case. Another limitation is in the calculation of the burden score, by

summing the scores it assumes that two drugs each with a rating of two would be equally ACh to one drug with a rating of 4.

Another approach that has been used is to multiply the atropine equivalent for a particular drug, as determined by antimuscarinic radioreceptor assay, by the total daily dosage and then sum the products to generate an ACh score (Tune et al., 1981, 1992; Francis et al., 1990).

Another method is to take the class of the drug and multiply it by daily effective dosage level number to give a drug risk number (Summers 1978). This method also attempts to classify drugs by their ACh properties or effects and assigns them a number (1-3). The class of drug was classified as class I- known synergistic effect with ACh agents, but not known as a direct cause of acute organic mental syndrome; II- known to cause delirium, but currently not documented to have CNS ACh properties; III- known to cause delirium reversed by CNS active anticholinesterases or known to have CNS ACh effect and to cause delirium. It then defines daily effective dosage based on a therapeutic dosage range given over a 24 hour period and assigns the dose a number. The criteria for daily effective dosage was defined as dosage level I- that dose range which would not give therapeutic effect for a 24 hour period; II- dose range which gives a therapeutic effect for a 24 hour period; III- dose range which exceeds the usual therapeutic range for a 24 hour period. It is these two assigned numbers that are multiplied together to calculate the drug risk number.

Schor et al., 1992, used a different approach for assessing ACh burden. In this study they used hospital admission records and counted each dose given, so that the tallied

number, indicating the total number of ACh drugs received by the patient, was equal to the total number of doses given. The limitation of this method did not take into account ACh exposure, dose exposure nor ACh binding affinity.

Marcantonio et al., 1994, studied dose response effect of benzodiazepines and ACh drugs and delirium in postoperative patients. They classified ACh exposure as either low or high depending on dose administered and whether or not it was given in single or multiple doses. The limitations with this method are it only looks at dose exposure, it does not take into account ACh potency or binding affinity.

Cao et al., 2006, in their calculation of ACh burden, normalized ACh exposure by taking the ACh dose given and dividing it by the sum of the ACh dose given with the minimum recommended daily dose.

In summary, there is not one standardized or universal method of measuring ACh burden. There have been multiple approaches and each has positive and negative characteristics. Finding a method that contains all of the positive characteristics of these methods and eliminates potential areas of subjectivity and has clinical utility would be ideal, but much research is still needed to create an ideal method of assessing ACh burden for clinicians caring for the geriatric population.

CHAPTER 3 Methodology

I. Subject/Patient Definition

A. Population

Hospitalized patients $\geq$ 65 years of age that have documented dementia as defined by ICD-9 codes (Appendex A) or inferred dementia based on use of drug therapy used in the treatment of dementia (Appendix A) during hospitalization were studied. This evaluation was conducted using the University Health System Consortium (UHC) Clinical Database. The UHC is an alliance of 90 academic health centers in the US. The UHC Clinical Database (CDB)-Pharmacy database contains a comprehensive collection of procedure and diagnoses-specific data derived from discharge abstract summaries and UB-92 data, coupled with specific medication use from charge transaction masters and patient billing files for all inpatients at participating (currently 42) centers. UHC maps members' charge transaction masters (CTM) drug descriptions into a common pharmacy lexicon, standardizing descriptions to achieve reporting at the fundamental drug level. Four quarters (12 months) of data was evaluated from October 2003 to September 2004. Data was available for this analysis through a data use agreement between Virginia Commonwealth University (VCU) and UHC. The data collection, analysis and reporting was consistent with this agreement and compliant with HIPAA privacy provisions. No

individual patient identifiers were maintained in the study data set to preserve patient and health system confidentiality. This study was reviewed by the VCU Office of Research Subject Protection Institutional Review Board and found to qualify for exemption from federal regulations requiring IRB review and approval. No safety reporting was performed because the study is a retrospective analysis of a dataset that does not contain individual patient and health system identifiers.

B. Sample Size

There are 12,481 hospitalized elderly patients $\geq$ 65 years of age with dementia. Of the 12,481 hospitalized elderly patients, 6926 were on ChEi therapy.

II. Study Design and Data Collection

A. Design

This study is a prevalence survey of ACh medication (Appendix B) use in a hospitalized setting in individuals $\geq$ 65 years of age with dementia on or not on ChEi therapy. Those on a ChEi and an ACh were compared to those on a ChEi and no ACh. Another comparison made was between those on an ACh and a ChEi to those on an ACh and no ChEi.

B. Data Collection

Patients $\geq$ 65 years of age in the database were subdivided into two mutually exclusive groups: 1) patients on ChEi therapy or NMDA therapy (Appendix A) use

during hospitalization and not receiving ACh (Appendix B), and 2) patients on ChEi or NMDA therapy (Appendix A) use during hospitalization and receiving ACh (Appendix B). The total number of patients in each group was determined. ACh medication use was determined for each patient in each group. The following ACh medications with central nervous system activity were included in this review (Piecoro et.al., 1998; Semla et.al., 2001): tricyclic antidepressants (amitriptyline, doxepin, imipramine, nortiptyline, desipramine), sedating antihistamines (diphenhydramine, promethazine, hydroxyzine), antiparkinson's drugs (benztropine, trihexyphenidyl), urinary antispasmodics (oxybutynin, tolterodine), gastrointestinal antispasmodics (atropine, scopolamine, hyoscyamine, belladonna alkaloids, dicyclomine), or antipsychotics (AP) (chlorpromazine, clozapine, promazine, thioridazine, olanzapine). The average dose per days of therapy and days of therapy for each centrally-acting ACh prescribed, length of stay (outcome measure), and potential confounders: age, sex, race, presence of delirium, from where they were admitted from (community, institutional setting, or transfer) and whether discharged to community or institutional setting was determined for each patient, and disease severity. The UHC database accounts for severity of illness and comorbid conditions variables (severity score) using a combination of the RDRGs and the UHC Complication Profiler (UCP) which is based on original research by Lisa Iezzoni at Beth Israel Hospital (Iezzone et al, 1992; Kalish et al.,, 1995; Iezzone et al.,, 1994). Four levels of severity are defined: Baseline (no substantial CCS), moderate CCS, major CCS, and catastrophic CCS (surgery).

All patients using ChEi during hospitalization were identified. The name of the ChEi, the average dose per day and the days of cholinesterase inhibitor therapy were determined for each patient. A flow chart describing the specific data elements collected can be found in Appendix C.

The entire population of dementia patients was used for specific aims 1, 2, and 3. It could not be determined by looking at the data whether 1) multiple strengths of the same drug for the same patient were given as one dose or as multiple doses or, 2) if those patients who may have received multiple doses of a drug with different days of therapy were being titrated up or off a medication or if there was some overlap between doses, these individuals were excluded from the remaining analyses to avoid assumptions that could possibly over or underestimate the calculated ACh burden score. In other words, patients who received more than one dose strength of an ACh medication during their hospital stay and the days of therapy were different from each other and from observed LOS were excluded from the analyses for specific aims 4, 5, 6, 7 and 8.

Patients included for the remaining analyses (specific aims 4, 5, 6, 7, and 8) were: 1) those who received one strength only for one ACh drug, or 2) those who received more than one ACh drug during their hospital stay and had multiple rows of data which had to be combined into one row per patient, or 3) those patients who received different strengths of an ACh drug but their days of therapy were the same as their observed LOS then the doses were combined and counted as one ACh drug and the combined dose was used in

calculating their ACh burden score. ACh burden was determined for each patient as dose [low, medium, high] x days of therapy x ACh potency [low, medium, high] summed across all ACh drugs. High doses were assigned a 3, medium assigned a 2, and low assigned a 1. Doses were defined using dosing recommendations for the elderly compiled in the Geriatric Dosage Handbook (Semla et al., 2005). Days of therapy was definded as: acute = $\leq$ 2 days of therapy and thus assigned a 1 or chronic being >2 days of therapy and thus assigned a 2 into the calculation. High ACh potency was assigned a 3, medium assigned a 2, and low ACh potency assigned a 1 for use in the above formula. ACh potency was estimated based on comparative drug tables compiled in the Geriatric Dosage Handbook (Semla et al., 2005) (AP, antidepressants, and antihistamines) and clinical pharmacology data in the published literature. The dose and potency definitions are in Appendix E.

Some of the variables in the data set had too many levels and therefore had to be condensed to fewer levels for the analyses, such as admission source had 18 levels, discharge status had 21 levels, and primary diagnosis had 1352 levels and were recoded as 3, 4, and 26 levels respectively. The definitions of how the variables were recoded for theses analyses can be found in Appendix D. There were no outliers excluded from the data analyses.

III. Data Analysis

All statistical analyses were performed using JMP 5.1. Assumptions of each test were checked before tests were performed. If the assumptions were not met then appropriate data transformations were performed. The significance level was set at 0.05.

A. Specific Aim #1

The first aim was to determine the prevalence of ACh medication use in hospitalized elderly patients $\geq$ 65 years of age with dementia. Prevalence of ACh drug use in patients with dementia was calculated by dividing the number of patients taking at least one ACh drug by the total number of patients with dementia (diagnosed and inferred). Characteristics of the groups were compared using tests of statistical significance appropriate for each variable type (Chi-square or t-test). The observed LOS was not normally distributed and therefore its log transformation was used for analyses and back transformed for reporting purposes.

$$\text{Prevalence of } ACh_{dementia} = \frac{\text{\# of dementia patients taking} \geq \text{1 ACh drug}}{\text{Total \# of dementia patients}}$$

B. Specific Aim #2

The second aim was to determine ACh prevalence in hospitalized elderly patients with dementia (Alzheimer's disease or other dementias) on ChEi. Prevalence of ACh drug use in patients with dementia and on ChEi therapy was calculated by dividing the number

of patients taking at least one ACh drug and a ChEi by the total number of patients taking a ChEi.

$$\text{Prevalence of ACh}_{\text{in ChEi dementia patients}} = \frac{\text{\# of patients on ChEi and} \geq 1 \text{ ACh drug}}{\text{Total \# of dementia patients on ChEi}}$$

C. Specific Aim #3

The next aim was to compare the ACh prevalence between hospitalized elderly patients with dementia using and not using ChEi therapy. Prevalences of hospitalized elderly patients taking ACh (dependent categorical (Y/N) variable) with or without a ChEi (independent categorical (Y/N) variable) were compared using χ^2.

D. Specific Aim #4

The fourth aim was to compare ACh burden between hospitalized elderly patients with dementia on and not on ChEi therapy.

The independent variable is ChEi therapy and is dichotomous, the dependent variable is ACh burden and was assessed as a continuous variable. Test for equal variances was done first to test for significant differences between group sizes. Since there was a significant difference, the t-test for unequal variances was used to assess the difference between the two groups.

If ACh burden is significantly different between groups then it would be expected that the total number of ACh drugs would also be different between groups. The total number of ACh drugs (dependent continuous variable) with a ChEi was compared to those

without a ChEi. Test for equal variances was done first to test for significant differences between group sizes. Since there was a significant difference the t-test for unequal variances was used to assess the difference between the two groups.

E. Specific Aim #5

The fifth aim was to characterize prescribing patterns of ACh medications in the hospitalized elderly, particularly those with dementia with or with out ChEi therapy.

The percentage use for each ACh drug in each group of patients, those with or without ChEi therapy, was calculated by dividing the number of courses of therapy for that drug in that group of patients by the total number of courses of therapy for all ACh drugs. A patient can have more than one course of therapy if they received more than one ACh drug during the hospitalization. Average daily dose and average days of therapy for each ACh drug was calculated to determine whether some medications are being used at higher or lower doses relative to their labeled dosage range.

F. Specific Aim #6

The following aim was to compare the prescribing patterns of urinary antispasmodics, GI antispasmodics, sedating antihistamines and antispychotics (AP) between hospitalized elderly patients with dementia using and not using ChEi therapy.

There are two different groups being analyzed, those using or using on ChEi therapy which is the independent dichotomous variable. Each group has the dependent

variables of urinary antispasmodics, GI antispasmodics, and AP and each was analyzed between groups using χ^2.

G. Specific Aim #7

The following aim evaluated and compared the impact of ACh medication use in hospitalized dementia patients on LOS, discharge status, and having delirium while in the hospital. A stepwise regression analysis was conducted to evaluate whether ACh use (categorical: yes/no) was associated with increased LOS in elderly patients with dementia. The dependent variable was log LOS and the independent variables evaluated were age, sex, race (White, Black, other (Asian, Hispanic, Native American/Eskimo, unknown), severity score (baseline/moderate/major/catastrophic), admission source (community/institution/other), discharge status (community/institution/other/died), and whether or not the patient was coded for delirium, received an ACh drug or received a ChEi. Criteria for the stepwise regression were defined as the probability of F or enter $\leq$ 0.05 and probability of F to remove $\geq$ 0.10.

Logistic regression analysis was used to evaluate the association between ACh medication use and discharge status (change from community to institution) and also whether or not the patient was documented as having delirium during their hospital stay.

H. Specific Aim #8

The last aim of the study was to evaluate and compare the impact of ACh burden in hospitalized dementia patients on LOS, discharge status, and having delirium while in the hospital.

For each group (ChEi with ACh and no ChEi with ACh), severity score, documented delirium, ACh burden, admission source, discharge to community/institution/ /other setting, age, race, and sex was incorporated as covariates in the regression model. ACh burden was assessed as a continuous independent variable for patients who received at least one ACh drug. It is expected that increasing exposure will be associated with increased LOS, change in discharge status between where they were admitted from and where they were discharged to, and having delirium while in the hospital.

The independent variable ACh burden and the dependent variable LOS was assessed as continuous variables and therefore was analyzed using a linear regression after log transformation of LOS.

Change in status between where they were admitted from and where they were discharged to was assessed as a dichotomous variable (institution, non-institution) and therefore analyzed using logistic regression.

Whether or not the patient was documented as having delirium while in the hospital was also assessed as a dichotomous variable and analyzed using logistic regression.

CHAPTER 4 Results

I. Specific aim #1

The first part of aim #1 was to compare characteristics between the groups and test for significance. Table 7 shows the characteristics of the study population at admission. There were 12,481 dementia patients with a mean age of 81.2 years, SD = 7.2 years with 60.3% of the population being female. This is representative of the elderly (≥65 years) population with dementia. Eighty-four percent of the dementia population was admitted from the community, of which 46.9% were admitted with a moderate severity score. The most common primary diagnosis was circulatory/vascular/heart disease in the dementia population.

The population characteristics were normally distributed. There were missing values listed as unknown (n=68) for severity scores in the data set. There were no significant differences in age ($p = 0.9$), sex ($p = 0.8$), race ($p = 0.4$), severity score ($p = 0.3$) nor admission source ($p = 0.6$) between the four groups (no ChEi with no ACh, no ChEi with ACh, ChEi and no ACh, or ChEi and ACh). The observed LOS was not normally distributed and therefore its log transformation was used in analyses.

Table 7. Population characteristics

	General Population	-ChEi		+ChEi	
		-ACh	+ACh	-ACh	+ACh
Age (years) Mean (± SD)	81.2 (± 7.2)	82.2 (± 7.4)	81.3 (± 7.4)	81.1 (± 6.9)	79.9 (± 6.9)
Sex % Female	60.3	64.7	62.2	56.2	59.4
Race % White	69.0	59.0	68.3	73.6	77.0
% Black	18.8	23.9	19.2	16.5	14.6
% Asian	1.1	1.3	0.9	1.2	0.8
% Hispanic	2.7	3.7	3.2	1.8	2.3
% other or unknown	8.4	12.0	8.4	6.9	6.6
Admission source:					
% Community	84.0	83.5	80.8	82.4	82.3
% Institution	14.6	14.1	14.9	14.4	15.1
% other	3.4	2.3	4.3	3.2	2.6
Severity score:					
% unknown	0.5	0.4	0.8	0.4	0.9
% baseline no substantial ccs	19.6	18.3	15.9	22.3	19.3
% moderate ccs	46.9	46.9	43.8	49.6	44.1
% major ccs	28.0	31.1	32.5	23.4	28.2
% catastrophic ccs (surgery)	5.0	3.3	7.1	4.3	7.5
% with documented delirium	5.5	7.3	8.9	3.5	4.2
Average LOS* (days) (SD, [95% CI])	4.9 (2.4, [4.8-5.0])	4.1 (2.3, [4.0-4.2])	6.0 (2.4, [5.7-6.2])	4.7 (2.4, [4.5-4.8])	6.2 (2.5, [6.0-6.4])
Primary Diagnosis (%)					
most common	circulatory/ vascular/ heart dz (19.7%)	circulatory/ vascular/ heart dz (18.1%)	circulatory/ vascular/ heart dz (18.4%)	circulatory/ vascular/ heart dz (21.1%)	circulatory/ vascular/ heart dz (20.6%)
2nd most common	respiratory infection/dz (11.1%)	respiratory infection/dz (14.0%)	dementia (11.3%)	respiratory infection/dz (10.0%)	dementia (9.6%)
3rd most common	dementia (10.1%)	dementia (11.3%)	respiratory infection/dz (11.1%)	dementia (8.8%)	mental/mood d/o (8.6%)
4th most common	gastrointestinal disease (6.2%)	UTI (7.4%)	gastrointestinal disease (8.8%)	fracture (5.3%)	respiratory infection/dz (8.1%)
total (n)	12,481	3,954	1,601	4,441	2,485

+ = yes; - = no

*Average LOS was calculated from the LOG transformation of LOS observed and then back transformed
dz = disease; d/o = disorder; ccs= complications & comorbidities

The second part of aim #1 was to determine the prevalence of ACh medication use in hospitalized elderly patients $\geq$ 65 years of age with dementia. There was a total of 4086 dementia patients who received at least one ACh drug during their hospitalization. The ACh prevalence among all dementia patients was 4086/12,481 = 32.7%. There was not a significant difference in ACh prevalence between those admitted from an institution and those admitted from the community.

II. Specific Aim #2

The second aim of the study was to determine ACh prevalence in hospitalized elderly patients with dementia on ChEi therapy. There were 2485 patients on ChEi therapy that also received at least one ACh drug. ACh prevalence in the dementia patients using ChEi therapy was 2485/6926 = 35.9% and 1601/5555 = 28.8% for those not using ChEi therapy.

There were a total of 7275 courses of ChEi therapy given. Table 8 shows the ChEi utilization for those also receiving ACh drugs and those not receiving ACh drugs.

Table 8. ChEi utilization by group

	-ACh			+ACh		
Drug	Frequency (%)	Average dose (mg)	Average therapy (days)	Frequency (%)	Average dose (mg)	Average therapy (days)
Donepezil	53.4	10.2	5.1	30.8	9.9	6.3
Galantamine	4.9	16.7	5.1	2.6	19.3	6.3
Rivastigmine	5.2	8.4	5.9	3.1	7.2	6.7
Tacrine	0.04	29.4	3	0.0	0.0	0.0

III. Specific Aim #3

The third aim was to test for significant differences in ACh prevalence between dementia patients on ChEi therapy and dementia patients not on ChEi therapy. Table 9 shows the total number of individuals in each group and the respective proportions receiving an ACh medication. There were 4086 dementia patients who received at least one ACh medication during their hospital stay. The ACh prevalence was significantly higher in the dementia patients who receive ChEi therapy than those who did not receive ChEi therapy (chi-square 70.1, df=q, $p < 0.0001$).

Table 9. Proportion receiving ACh within each group

	count (proportion)	received ACh: No	received ACh: Yes	total
received ChEi	No	3954 (.471)	1601 (.392)	5555 (.445)
	Yes	4441 (.529)	2485 (.608)	6926 (.555)
	total	8395 (1.0)	4086 (1.0)	12481 (1.0)

IV. Specific Aim #4

The next aim of the study was to compare ACh burden between hospitalized elderly patients with dementia using and not using ChEi therapy. After excluding those patients who received multiple different doses of an ACh that had different days of therapy from each other and from the observed length of stay, there were 3486 patients remaining of the original 4086 patients for this analysis. Table 10 shows the mean total number of ACh drugs and ACh burden for dementia patients taking and not taking ChEi therapy.

ACh burden was compared between ACh with ChEi and ACh with no ChEi, using Welch ANOVA due to a significant difference between the group sizes ($F(1, 3180.6) = 9.9$, $p = 0.0017$). When using the t-test for unequal variance, ACh burden was significantly higher (difference = 0.5, 95%CI [0.2, 0.8], $p = 0.0017$) in those patients receiving a ChEi than those who were not receiving a ChEi.

The total number of ACh medications was compared using Welch ANOVA and were found to be significantly different ($F(1, 3176.7) = 8.9$, $p = 0.0029$). When using the t-test for unequal variance, the total number of ACh drugs was higher in patients receiving ChEi than those who were not (difference = 0.05, 95% CI [0.02, 0.08], $p = 0.0029$).

Table 10. ACh medication use

		mean	std dev	95% CI	
dementia pts +ChEi					
	# ACh drugs	1.2	0.5	1.18	1.23
	ACh burden	7.1	4.9	6.9	7.3
dementia pts -ChEi					
	# ACh drugs	1.2	0.4	1.1	1.2
	ACh burden	6.6	4.3	6.4	6.9

V. Specific Aim #5

The purpose of this aim was to characterize prescribing patterns of ACh medications used in the hospitalized elderly, particularly those with dementia with or with out ChEi therapy. There were 5510 ACh courses given to 3486 hospitalized elderly patients with dementia. Table 11 shows the frequency of use for a particular ACh drug and its average dose and days of therapy for dementia patients that did or did not receive ChEi

therapy. The most frequently used ACh drugs were: tolterodine 4.4%, oxybutynin 6.4%, atropine 7%, promethazine 12.2%, olanzapine 16.8%, and diphenhydramine 19.7%. Olanzapine, tolterodine, and oxybutynin were given chronically (average days of therapy were approximately 5 for each) and accounted for 27.6% of all prescribed ACh, whereas atropine, promethazine and diphenhydramine were mainly given acutely (average days of therapy were approximate 1.5 for each) and accounted for 38.9% of all prescribed ACh. The average dose for most of the ACh drugs given were less than the suggested recommended maximum dosage per the Geriatric handbook. The average diphenhydramine dose was nearly double and average clozapine was nearly triple the recommended maximum dosage listed in the Geriatric handbook. The average promazine and nortriptyline doses given were also higher than the recommended maximum dosage listed in the Geriatric handbook. The average doses of oxybutynin and tolterodine given were slightly higher than the recommended maximum dosage listed in the Geriatric handbook.

Table 11. ACh prescribing patterns

	+ChEi				-ChEi			
ACh Drug	frequency (%)	Ave. dose (mg)‡	95% CI (dose)	Ave. tx (days)	frequency (%)	Ave. dose (mg)‡	95% CI (dose)	Ave. tx (days)
Amitriptyline	1.0	53	36.8, 69.3	5	0.6	37.5	27.7, 47.3	5.3
Atropine	3.5	1.0	0.8, 1.1	1.1	2.5	1.3	1.0, 1.5	1.2
Atropine/ diphenoxylate	0.7	2.6 ea	1.9, 3.3	3.5	0.3	3.1 ea	1.5, 4.7	6.3
Atropine/hyoscyamine / scop/pheno	0.1	1.5 ea	0.9, 2.1	1.0	0.1	1.7 ea	1.1, 2.2	1.0
Belladonna/opium supp	0.3	1.3 ea	1.1, 1.5	1.8	0.1	1.3 ea	0.6, 1.9	1.2

(Table 11 continued from page 49)

	+ChEi				-ChEi			
ACh Drug	frequency (%)	Ave dose (mg)‡	95% CI (dose)	Ave tx (days)	frequency (%)	Ave dose (mg)‡	95% CI (dose)	Ave tx (days)
Benztropine	0.8	1.5	1.1, 2.0	4.7	0.8	1.5	1.2, 1.8	3.9
Chlorpromazine	0.3	48.2	21.2, 75.2	2.3	0.2	77.7	43.2, 112.2	2.0
Clozapine	0.1	83.1	39.6, 126.6	4.7	0.04	270.6	181.3, 360.0*	4.5
Desipramine	0.1	83.3	22.0, 144.7	3.2	0.0	0.0	0.0†	0.0
Dicyclomine	0.1	28.6	19.2, 37.9	4.1	0.05	21.7	10.0, 36.0*	6.0
Diphenhydramine	11.6	44.8	42.7, 46.9	1.5	8.1	45.4	42.8, 48.0	1.5
Doxepin	0.3	61.0	27.1, 94.8	5.7	0.04	19.2	13.3, 25.0*	5.0
Hydroxyzine	0.7	58.8	40.0, 77.6	2.6	0.5	65.0	34.4, 95.5	1.9
Hyoscyamine	0.3	0.4	0.3, 0.5	4.4	0.1	0.4	0.3, 0.6	4.4
Imipramine	0.2	39.7	28.0, 51.5	5.5	0.1	53.8	15.4, 92.1	2.8
Nortriptyline	0.7	44.5	27.0, 62.0	3.8	0.4	40.1	24.9, 55.2	4.3
Olanzapine	9.8	7.3	6.6, 8.0	5.3	7.0	8.3	6.1, 10.5	4.5
Oxybutynin	4.4	11.0	9.6, 12.3	4.9	2.0	10.9	8.7, 13.0	4.3
Promazine	0.02	75.0	75.0†	1.0	0.04	25.0	25.0†	1.0
Promethazine	7.6	33.3	31.5, 35.1	1.6	4.6	29.7	28.2, 31.2	1.7
Scopolamine	0.09	0.7	0.2, 1.3	1.4	0.07	1.2	0.2, 2.2	3.3
Thioridazine	0.1	91.0	9.6, 172.4	4.6	0.05	95.1	22.9, 187.5*	4.3
Tolterodine tartrate	3.1	5.8	4.4, 7.2	4.6	1.3	5.0	3.3, 6.7	4.5
Trihexyphendyl	0.1	6.9	2.0, 29.0*	4.8	0.1	4.2	0.9, 7.6	2.9

‡ dosage is in mg except where otherwise noted
* when the lower 95% CI was 0 due to their being only a few doses with wide spread, the 95% CI was entered as the minium and maximum dosages
† there was either no doses, one dose, or two doses given at the same dose
Ave= average; tx= therapy

VI. Specific Aim #6

The purpose of this aim is to compare the prescribing patterns for the ACh classes: urinary antispasmodics, GI antispasmodics, sedating antihistamines and ACh antispychotics between hospitalized elderly patients with dementia on and not on ChEi

therapy. Table 12 shows the number of patients in each group, those receiving and not receiving ChEi therapy, that received at least one ACh dose from each ACh class. There were no significant differences in the proportion of AP ($p = 0.6$), GI antispasmodics ($p = 0.7$), nor sedating antihistamines ($p = 0.4$) doses given between hospitalized dementia patients receiving and not receiving ChEi therapy. There was a significant difference in the proportion of urinary antispasmodics ($p < 0.0001$) given between hospitalized dementia patients receiving and not receiving ChEi therapy.

Table 12. Proportion receiving ACh class per group

ACh drug class	-ChEi	+ChEi	total
Antipsychotic	455 (0.40)	678 (0.60)	1133
GI antispasmodic	178 (0.39)	282 (0.61)	460
Sedating antihistamine	1098 (0.52)	1011 (0.48)	2109
Urinary antispasmodic	177 (0.30)	407 (0.70)	584

VII. Specific Aim #7

Aim #7 evaluated and compared the impact of ACh medication use in hospitalized dementia patients on LOS, discharge status, and having delirium while in the hospital. There were 11,881 of the original 12,481 patients for this analysis after excluding 600 who had received multiple different ACh doses with different days of therapy from each other and from the observed LOS. An additional 60 patients were omitted from the analyses because of missing severity score values. Table 13 is a correlation matrix that shows the relationships among the study variables.

Table 13. Correlations among independent and dependent variables

	Age (yrs)	Race	Received ACh	Received ChEi	Severity Score	Admission Source	Discharge Status	Log LOS obsvd	Sex	Patient coded for delirium
Age (yrs)	1.00									
Race	-0.055 p<.0001	1.00								
Received ACh?	-0.065 p<.0001	-0.068 p<.0001	1.00							
Received ChEi?	-0.082 p<.0001	-0.14 p<.0001	0.069 p<.0001	1.00						
Severity Score	0.020 p=.03	-0.010	0.069 p<.0001	-0.051 p<.0001	1.00					
Admission Source	-0.0009	-0.007	0.0036	-0.017 p=.05	-0.0043	1.00				
Discharge Status	0.11 p<.0001	-0.031 p=.002	0.026 p=.004	-0.11 p<.0001	0.23 p<.0001	0.0044	1.00			
Log LOS obsvd	-0.047 p<.0001	0.010	0.12 p<.0001	0.060 p<.0001	0.28 p<.0001	0.011 p<.0001	0.17 p<.0001	1.00		
Sex	0.14 p<.0001	0.043 p<.0001	0.0022 p<.0001	-0.07 p<.0001	-0.036 p<.0001	0.0057 p<.0001	0.0005 p<.0001	-0.031 p<.0001	1.00	
Patient coded for delirium?	0.014	-0.017	0.0067	-0.091 p<.0001	0.013	0.0017	0.024 p=.01	0.054 p<.0001	-0.023 p=.01	1.00

A. ACh impact on LOS

The results from specific aim #3 showed that there was a significant difference between ACh use for those who receive or do not receive ChEi therapy. ANOVA was performed to test the significance of an interaction between ChEi therapy and ACh medication use with LOS. Since there was evidence of a non-ignorable interaction (p=.0008), of whether or not one received an ACh or a ChEi therapy on LOS, the effect of one factor will be considered separately for each level of the other factor. The effect of ChEi therapy will first be considered within the two ACh groups. Within the subgroup of patients without ACh therapy, there was a significant difference in LOS depending upon whether they received ChEi therapy (unadjusted p<.0001, Bonferonni cut-off = .0125),

those that received ChEi therapy had a LOS of 1.2 days longer (SE= 1.0). Within the subgroup of patients who received an ACh there was no significant difference in LOS depending upon whether or not they received ChEi therapy (unadjusted p=.03, Bonferonni cut-off = .0125). Within the subgroup of patients who did not receive a ChEi there was a significant difference in LOS depending upon whether or not they also received an ACh drug (unadjusted p<.0001, Bonferonni cut-off =.0125), those that also received an ACh had a LOS of 1.3 days longer (SE=1.0). Within the subgroup of patients who did receive a ChEi there was a significant difference in LOS depending upon whether or not they also received an ACh drug (unadjusted p<.0001, Bonferonni cut-off = .0125), those that received an ACh had a stay of 1.1 days longer (SE=1.0).

The above results were confirmed by repeating the analysis with the independent variable as group (no ACh with no ChEi; no ACh with ChEi; ACh with no ChEi; and ACh with ChEi) and the groups were compared with Tukeys HSD multiple comparison. Further analysis on the variables and the three most prevalent diagnosis on admission were compared between subgroups to further explain these results.

Those with no ACh therapy (n=8395) with their ChEi therapy, had a significantly longer LOS than those who did not receive ChEi therapy. Those on ChEi therapy were significantly younger and white (p<.0001), were less likely to be coded for delirium (p<.0001), were significantly more likely to have a severity score of 4 (catastrophic), 2 (moderate), or 1 (baseline) (p<.0001), and more likely to be discharged to either the community or other (other, unknown, transfer). Also the proportion of men compared to the proportion of women was significantly higher for those not on an ACh (p<.0001).

Those on a ChEi were significantly more likely to be admitted for circulatory/vascular/heart disease ($p<.0001$).

In those patients who were not on ChEi therapy ($n=5331$) but received at least one ACh had a significantly longer LOS than those who did not receive an ACh. They were also significantly younger ($p=.0003$), more likely to be white ($p<.0001$), significantly more likely to have a severity score of 3 (major) or 4 (catastrophic) ($p<.0001$), and more likely to be admitted for circulatory/vascular heart disease ($p=.02$). There was a significant difference in discharge status ($p=.02$) depending on whether or not they were also taking an ACh. Those on ACh were more likely to have a discharge status of 3 (other, unknown, transfer) or 4 (expired) ($p=.02$), those not on ACh were more likely to be discharged to the community, but there were no significant differences in discharge status to an institution whether or not they received an ACh.

In those patients who were on ChEi therapy ($n=6550$) but received at least one ACh had a significantly longer LOS than those who did not receive an ACh. They were also significantly younger ($p<.0001$), more likely to be white ($p<.01$), a significantly larger proportion were female ($p<.03$), and significantly more likely to have a severity code of 3 (major) or 4 (catastrophic). They was a significant difference in discharge status ($p=.006$) depending on whether or not they were also taking an ACh. Those on ACh were more likely to have a discharge status of 3 (other, unknown, transfer) or 4 (expired), those not on ACh were more likely to be discharged to the community, but there were no significant differences in discharge status to an institution whether or not they received an ACh.

A dose-response relationship with ACh administration (diphenhydramine) has previously established a significantly longer hospital stay (Agostini et al., 2005).

To further confirm the above differences between groups, stepwise multiple linear regression was used to evaluate the impact of ACh medication use on LOS. ChEi therapy and the ACh-ChEi interaction were put into the stepwise regression model because of its significant interaction between the two. Independent variables entered the stepwise regression model in the following order: severity score, discharge status, whether or not they received an ACh, whether or not they received a ChEi, age, whether or not they coded for delirium, race, and then the ACh-ChEi interaction. The first three variables account for the majority of the change in the r^2. Whether or not they received a ChEi and the ACh-ChEi interaction added 0.54% and 0.08% respectively, of the variability accounted for in the model. The model accounts for approximately 14% of the variability in LOS (r^2 = 0.1433) for elderly patients with dementia. The table 14 shows the median and average LOS for each of the groups. The model summary output from JMP is in Table 15.

Table 14. LOS comparison between groups

Group	median (days)	mean (days)	95% CI	
-ACh -ChEi	4.0	5.9	5.7	6.1
-ACh +ChEi	5.0	6.8	6.6	7.1
+ACh -ChEi	6.0	8.2	7.7	8.7
+ACh +ChEi	6.0	8.4	8.0	8.8

Table 15. Model summary of ACh use (Y/N) with Response: LOS

Stepwise Fit

Response:
Log LOS obsvd

Stepwise Regression Control

Prob to Enter	0.050
Prob to Leave	0.100

60 rows not used due to missing values (severity score).

Current Estimates

SSE	DFE	MSE	RSquare	RSquare Adj	Cp	AIC
1466.6884	11807	0.1242219	0.1433	0.1424	15.540933	-24640.9

Lock	Entered	Parameter	Estimate	nDF	SS	F Ratio	Prob>F
X	X	Intercept	1.0074885	1	0	0.000	1.0000
	X	Age (yrs)	-0.003034	1	5.336063	42.956	0.0000
		Sex 2{2-1}	0	1	0.143045	1.152	0.2832
	X	Race 2{1-2&3}	-0.0150357	2	2.221552	8.942	0.0001
	X	Race 2{2-3}	-0.009303	2	2.221552	8.942	0.0001
	X	Received ACh?{NO-YES}	-0.0392774	1	14.38638	115.812	0.0000
	X	Recieved ChEi?{NO-YES}	-0.0257152	1	5.988514	48.208	0.0000
	X	Received ACh?{NO-YES}*Recieved ChEi?{NO-YES}	-0.0122351	1	1.416281	11.401	0.0007
	X	Patient coded 4delirium?{NO-YES}	-0.0424449	1	4.269739	34.372	0.0000
	X	Severity Score 2{1&2-3&4}	-0.1378355	3	114.0869	306.137	0.0000
	X	Severity Score 2{1-2}	-0.0278838	3	114.0869	306.137	0.0000
	X	Severity Score 2{3-4}	-0.1025714	3	114.0869	306.137	0.0000
		Admission Source 2{1&2-3}	0	2	0.414475	1.668	0.1886
		Admission Source 2{1-2}	0	2	0.414475	1.668	0.1886
	X	Discharge Status 2{1-4&2&3}	-0.0441862	3	62.72743	168.321	0.0000
	X	Discharge Status 2{4-2&3}	-0.0542619	3	62.72743	168.321	0.0000
	X	Discharge Status 2{2-3}	0.00921026	3	62.72743	168.321	0.0000

Step History

Step	Parameter	Action	"Sig Prob"	Seq SS	RSquare	Cp	p
1	Severity Score 2{1-2}	Entered	0.0000	148.9621	0.0870	772.12	4
2	Discharge Status 2{1-4&2&3}	Entered	0.0000	58.00988	0.1209	311.07	7
3	Received ACh?{NO-YES}	Entered	0.0000	15.70859	0.1301	186.6	8
4	Recieved ChEi?{NO-YES}	Entered	0.0000	9.253148	0.1355	114.1	9
5	Age (yrs)	Entered	0.0000	5.769217	0.1388	69.654	10
6	Patient coded 4delirium?{NO-YES}	Entered	0.0000	4.167696	0.1413	38.099	11
7	Race 2{1-2&3}	Entered	0.0002	2.130845	0.1425	24.944	13
8	Received ACh?{NO-YES}*Recieved ChEi?{NO-YES}	Entered	0.0007	1.416281	0.1433	15.541	14

B. ACh impact on delirium

A chi-square of ACh drug use (Y/N) verses whether or not a patient coded for delirium showed no significant difference (p = .47). A logistic regression was used to

evaluate the impact of ACh medication use and whether or not the patient was coded for delirium, first with ACh use alone and then including the ACh-ChEi interaction.

Even after taking into account the other variables, ACh medication use was still not significant in whether a patient coded for delirium or not ($p=.66$). When analysis was repeated taking into account ChEi use and the ACh-ChEi interaction, ACh medication use became even more non significant in whether a patient coded for delirium or not ($p=.74$). The ACh-ChEi interaction was also non-significant ($p=.51$) but ChEi use was significant ($p<.0001$). ACh medication uses' lack of significance could be due to the inability from the database to differentiate whether or not the ACh drug was being used to treat delirium, such the case with the use of many AP or if it was causing the delirium. The lack of significance could also be due to whether or not a patient actually gets documented as having delirium during their hospital stay. Accurate documentation of delirium relies heavily upon patient records and not billing codes. In the 11,881 patients used in this analysis, only 5% of the patients were documented as having delirium, which is grossly understated compared to numerous studies which document 14-56% (Rosin 1966; Hodkinson 1973; Bergman 1974; Seymour 1980; Chisholm 1982).

C. ACh impact on discharge status

Chi-square indicated a significant difference ($p=.05$) between community-dwelling elders discharged to either community or an institution depending on whether or not they received an ACh drug. There is a greater likelihood of being discharged to an institution if

they received an ACh drug (p=.03). A logistic regression was used to evaluate the impact of ACh medication use on discharge status, first ACh use alone and then including the ACh-ChEi interaction.

After taking into account the other variables, ACh medication use was no longer significant (p = .49). When the analysis was repeated to include ChEi and the ACh-ChEi interaction, ACh medication use became even more non- significant (p = .98). The ACh-ChEi interaction was also non-significant (p=.20), but ChEi use was significant (p<.0001).

VIII. Specific Aim #8

The purpose of this last aim was to further evaluate the impact of ACh burden in hospitalized dementia patients on LOS, discharge status, and having delirium while in the hospital. ACh burden was slightly skewed to the left (median = 6, range [2, 36]) and therefore its log was used in the following analyses.

A. ACh burden and LOS

A stepwise multiple linear regression will be used to evaluate the impact of ACh burden on LOS. Since it was previously shown that ACh use impacts LOS, this analysis attempted to look at a dose response relationship in only those patients who received at least one ACh drug. Independent variables entered the stepwise regression model in the following order: severity score, log ACh burden score, discharge status, whether or not they coded for delirium, age, race. The first three variables account for the majority of the

change in the r^2. The model accounts for approximately 17% of the variability in LOS (r^2 = 0.1701) for elderly patients with dementia. The model summary output from JMP is in Table 16.

Table 16. Model Summary of ACh burden with Response: LOS

Stepwise Fit
Response:
Log LOS obsvd

Stepwise Regression Control
Prob to Enter 0.050
Prob to Leave 0.100

8428 rows not used due to missing values (did not receive an ACh drug).

Current Estimates

SSE	DFE	MSE	RSquare	RSquare Adj	Cp	AIC
426.78412	3440	0.1240652	0.1701	0.1672	14.194673	-7193.26

Lock	Entered	Parameter	Estimate	nDF	SS	F Ratio	Prob>F
X	X	Intercept	0.8759619	1	0	0.000	1.0000
	X	Age (yrs)	-0.0027249	1	1.224588	9.871	0.0017
		Sex{FEMALE-MALE}	0	1	0.000041	0.000	0.9854
	X	Race 2{1-3&2}	-0.0268216	2	1.797161	7.243	0.0007
	X	Race 2{3-2}	0.00760512	2	1.797161	7.243	0.0007
	X	Recieved ChEi?{NO-YES}	-0.0140357	1	0.618889	4.988	0.0256
	X	Patient coded 4delirium?{NO-YES}	-0.0556219	1	2.229484	17.970	0.0000
	X	Severity Score 2{1&2-3&4}	-0.1398231	3	41.64367	111.887	0.0000
	X	Severity Score 2{1-2}	-0.0415147	3	41.64367	111.887	0.0000
	X	Severity Score 2{3-4}	-0.0819861	3	41.64367	111.887	0.0000
		Admission Source 2{1&2-3}	0	2	0.520225	2.098	0.1229
		Admission Source 2{1-2}	0	2	0.520225	2.098	0.1229
	X	Discharge Status 2{1-2&4&3}	-0.0635743	3	13.91543	37.387	0.0000
	X	Discharge Status 2{2-4&3}	0.00478758	3	13.91543	37.387	0.0000
	X	Discharge Status 2{4-3}	-0.0371331	3	13.91543	37.387	0.0000
	X	Logburden	0.10300177	1	13.22582	106.604	0.0000

Step History

Step	Parameter	Action	"Sig Prob"	Seq SS	RSquare	Cp	p
1	Severity Score 2{1&2-3&4}	Entered	0.0000	54.6154	0.1062	260.94	4
2	Logburden	Entered	0.0000	14.4715	0.1343	146.26	5
3	Discharge Status 2{1-2&4&3}	Entered	0.0000	12.72522	0.1591	49.653	8
4	Patient coded 4delirium?{NO-YES}	Entered	0.0001	1.915204	0.1628	36.211	9
5	Age (yrs)	Entered	0.0005	1.512172	0.1658	26.018	10
6	Race 2{1-3&2}	Entered	0.0017	1.591616	0.1689	17.185	12
7	Recieved ChEi?{NO-YES}	Entered	0.0256	0.618889	0.1701	14.195	13

B. ACh burden and delirium

A chi-square of ACh burden verses whether or not a patient coded for delirium showed no significant difference ($p = .34$). Even after taking into account the other variables, ACh burden still was not significant in whether a patient was coded for delirium or not ($p = .14$).

C. ACh burden and discharge status

A logistic analysis of ACh burden (continuous variable) verses change in discharge status (community or institution) in community dwelling elderly showed no significant difference ($p = .34$). Even after taking into account the other variables, ACh burden still was not significant in discharge status of community dwelling elderly ($p = .8$).

Chapter 5 Conclusions/Discussion

I. Conclusion

A. ACh prevalence

A1. Prevalence among hospitalized elderly dementia patients

In this study, 32.7% of the hospitalized elderly patients received an ACh. This is consistent with past studies that have looked at prevalence of ACh use in nursing home patients. The Medicare utilization review found that 34.5% of patients were receiving ACh drugs (Seifert et al., 1983). Another study that looked at diphenhydramine use only, among hospitalized elderly patients found that 27% had received diphenhydramine during their hospital stay (Agostini et al., 2005). Blazer et al., reported that nearly 60% of nursing home residents and 23% of elderly people living in the community received drugs with ACh activity.

A2. Prevalence among hospitalized elderly dementia patients on ChEi therapy

ACh prevalence among the dementia patients on ChEi therapy was 28.8% which is consistent with the findings of past studies. Past studies that looked at state Medicaid administrative data claims found 13.5% and 35.4% of patients receiving a ChEi were also receiving an ACh drug (Slattum et al., 2001; Carnahan et al., 2004). Kogut et al looked at

the prevalence of community and LTC residents (≥ 45) that were enrolled in the Rhode Island Medicaid program who were dispensed a ChEi and a drug therapy that can impair cognition (list of 58 drugs). Nearly 60% of those receiving a ChEi also received drug therapy that can impair cognition (40 of the 58 drugs had ACh properties) (Kogul et al., 2005). In a study by Carnahan et al., 35.4% of individuals of Iowa Medicaid beneficiaries (≥ 50) taking ChEi were also concurrently receiving an ACh drug (Carnahan et al., 2004). ACh drugs such as those used to treat urinary incontinence are frequently started after initiation of ChEi therapy.

A3. Comparison between those on and not on ChEi therapy

The prevalence of ACh drug use in this study was significantly higher in those patients who were receiving ChEi therapy compared to those who were not. Gill et al., found patients who were receiving ChEi therapy were 4.5% more likely to be prescribed an ACh medication than those not on a ChEi. Community-based elderly taking ChEi are more likely to receive an ACh and nearly one third of those taking a ChEi were also receiving an ACh (Gill et al., 2005). In this study there were no significant differences in ChEi therapy between those from the community and those from an institution ($p = .53$).

B. Comparison of ACh burden between those on and not on ChEi therapy

The ACh burden was significantly higher in those patients on a ChEi compared to those individuals who were not on ChEi therapy. Since ACh burden was higher, it was a logical progression that the total number of ACh drugs would also be significantly higher.

This would seem to make sense since current literature suggests that it is likely to be prescribed more than one ACh drug while on ChEi therapy. The total number of ACh drugs received by an individual on ChEi therapy was significantly higher than those patients not on ChEi therapy ($p = .0029$). The study by Roe et al., that looked at community-dwelling elderly, pharmacy benefit management claims, of the 33% that were receiving an ACh, 26 % of them were also taking more than one ACh drug (Roe et al., 2002).

C. ACh prescribing patterns

Olanzapine, tolterodine, and oxybutynin were given chronically (average days of therapy were approximately 5 for each) and accounted for 27.6% of all prescribed ACh, whereas atropine, promethazine and diphenhydramine were mainly given acutely (average days of therapy were approximate 1.5 for each) and accounted for 38.9% of all prescribed ACh. The most commonly used ACh drugs were the ones used for acute or prophylactic therapy, promethazine and diphenhydramine together accounted for 32%, diphenhydramine alone was almost 20% of all ACh prescribed. This is not surprising and is similar to the similar results as Beers et al., and Agostini et al., In an outpatient study of elderly patients of intermediate-care facilities in Massachusetts, more than 25% of them received some form of a sedative and/or hypnotic medication, with diphenhydramine accounting for 26% (14-41% over all study sites) (Beers et al., 1988). In a study of hospitalized medical patients 70 years and older, 27% had received diphenhydramine during their hospitalization (Agostini et al., 2005).

There were no significant differences in the proportion of AP, GI antispasmodics nor sedating antihistamine use between those on and not on ChEi therapy, but there was a significant difference in the proportion of urinary antispasmodics that were prescribed between the two groups. Those receiving ChEi were significantly more likely to also receive a drug for urinary incontinence (oxybutynin or tolterodine). Use of cholinesterase inhibitors has been associated with an increased risk of receiving an ACh drug to manage urinary symptoms (Gill et al 2005; Roe et al., 2002).

D. ACh impact on LOS, delirium, and discharge status

D1. LOS

Since ACh and ChEi did not have independent effects, their separate effects on LOS could not be distinguished. When comparing the groups (no ACh with no ChEi, no ACh with ChEi, ACh with no ChEi, and ACh with ChEi) there was a significant difference in LOS across groups. There was not a significant difference in LOS in the subgroup of people taking an ACh with or without ChEi therapy. When put into order of group by its effects on LOS in equation form it looks like this:

(ChEi with ACh) = (no ChEi with ACh) > (no ACh with ChEi) > (no ACh and no ChEi)

When multiple regression was performed the variables that had the greatest significant effect on LOS were severity scores, discharge status, whether or not they were taking an ACh, age and delirium and accounted for 15% of the variablity. The low

variability of the results observed could be due to a number of things. Many of the variables and response variables were significantly correlated with each other as per Table 13. There is a significant interaction of ACh and ChEi drug use and also the fact that this model only took into account the variables for which data was collected on and not all variables that could possibly affect LOS.

There was a significant difference in LOS between patients who did or did not experience delirium during their hospital stay ($p<.0001$), those that experienced delirium had a significantly longer LOS than those who did not. There was also a significant difference in LOS depending on where a patient was discharged to.

D2. Delirium

In this study it was found that only 5% of the population was documented as having delirium, which is grossly understated and could explain why no significant difference was found between ACh drug use nor ACh burden and whether or not a patient was coded for having delirium during their hospital stay. There have been numerous studies which have documented the occurrence of delirium in 14-56% of hospitalized elderly patients (Rosin 1966; Hodkinson 1973; Bergman 1974; Seymour 1980; Chisholm 1982). One reason for the under documentation of delirium is that documentation of (Y/N) delirum relied on patient records and not a billing code.

The inability to discern a direct relationship of ACh use or burden to delirium could be due to a number of things. The method used to measure ACh burden most likely was not sensitive enough. There was a case-control study (Marcantonio et al., 1994), a

prospective study (Francis et al., 1990) and a cohort analytic study (Schor et al., 1992) that were also unable to find a direct relationship between ACh use and delirium. These studies documented delirium based on the patient meeting CAM, DSM-III, with or without MMSE criteria and ACh use by either counting total number of doses received or noting whether or not the patient received an ACh drug. There have been 14 studies that have found a significant relationship between ACh drug use and the development of delirium all used either SAA, plasma ACh activity, or multiplying the atropine equivalents of the drug by the total daily dosage given and then summing them all for each ACh drug given to measure ACh burden. They also used at least one of several tests (Delirium symptom interview, battery of mental or psychological tests, DSM-III, CAM, or Cognitive performance scale) in documenting delirium.

D3. Discharge status

ACh use alone was significant in determining discharge status of community-dwelling elders to either community or an institution, but when other variables where taken into account, ACh use lost its significance. The ACh burden calculation was also found to be non-significant in determining discharge status. This could also possibly be due to many of the variables and response variables being significantly correlated with each other as per Table 13. Significant differences existed between those discharged to a community and those either discharged to an institution, other, or expired ($p<.0001$). There was also a significant difference between whether or not an individual experienced delirium and where they were discharged to ($p<.0001$). Those that did not experience delirium were

more likely to be discharged to the community or expired compared to those that experienced delirium who were more likely to be discharged to either an institution or other.

II. Limitations

This study used data that was collected from large teaching hospitals, which may not reflect the prescribing patterns of community hospital doctors.

Another limitation is in the ACh burden calculation by defining duration of therapy as either acute or chronic. The way acute ($\leq$ 2 days) and chronic (>2 days) use was defined is arbitrary. From the data set it cannot be differentiated when the doses were given. For example, if someone received more than one dose and the days of therapy were less than their observed LOS, one cannot tell if those doses were given consecutively or if they were days apart. Another limitation of how the burden score was calculated is in summing the scores of each ACh drug received by a patient. The summing assumes that two drugs each with a rating of two would be equally ACh to one drug with a rating of 4. It is unknown if taking multiple ACh drugs if each drug's effect is additive or if there is a certain threshold and once that point is met the addition of anymore drugs will not exert any additional effect or if it could exert an exaggerated effect, the relationship could be synergistic. The calculation may have been more accurate if the dose was multiplied by atropine equivalents but that data was only available on four of the 31 drugs in the literature.

Another limitation is the poorly documentation of delirium. Because it is a database study, it cannot be distinguished when the ACh drug was given in relation to

when the patient developed delirium. It is not possible to differentiate whether or not the ACh drug was used to treat delirium, such as the case with the use of many AP, or if it was causing the delirium. Also, because this is an observational study it cannot establish causation.

III. Discussion:

Use of cholinesterase inhibitors has been associated with an increased risk of receiving an ACh drug to manage urinary symptoms (Gill et al 2005; Roe et al., 2002). Multiple studies have found that approximately 33% of those on ChEi are also receiving an ACh. Not only are those on ChEi at an increased risk (Gill et al., 2005) of being prescribed an ACh, it is common to find them on more than one ACh drug (Roe et al., 2002).

Medications have been implicated in at least 40% of delirium cases in hospitalized elderly patients (Francis et al., 1990). Time and time again, numerous studies have associated delirium with significantly increased adverse outcomes such as mortality, significantly increased LOS, institutionalization, and functional disability (Thomas et al., 1988; Francis et al 1990, 1992; Levkoff et al., 1992; Inouye et al., 1993; Murray et al., 1993; Rockwood 1993), which are significant human and economic burdens.

Carnahan et al found that nearly 75% of all ACh prescribed were inappropriate for use in the elderly and of those 22% were inappropriate under any circumstance (Carnahan et al 2004). Another study by Agostini documented nearly 24% of all diphenhydramine doses given to hospitalized elderly patients as inappropriate (Agostini et al., 2005).

Inappropriate use was defined as given as transfusion prophylaxis without prior documentation of having a previous reaction or given to individuals with obstructive urinary symptoms. In this study nearly 39% of all ACh drugs were given acutely and 32% of them given were diphenhydramine alone.

There has only been one study conducted that looked at the prevalence of one ACh, diphenhydramine, use in hospitalized elderly patients, in one hospital and its effects on LOS and delirium. In that study, Agostini et al., found that the diphenhydramine exposed group was at an increased risk for delirium, urinary catheter placement, and longer median LOS. The dose-response relationship demonstrated a significant trend toward increased cognitive decline and delirium symptoms with increasing dose.

The majority of studies that looked at the prevalence of concomitant use of ChEi therapy and ACh have been done with Medicaid administrative claims, which were performed before Medicaid Part D, may not be fully representative of this population. This study looked at billing data that was acquired from the UHC database which includes data from the 42 participating teaching hospitals.

Thus far this is the first study to examine the ACh prevalence of more than one ACh drug (31 total), in hospitalized elderly dementia patients, diagnosed or inferred, that are or are not concurrently taking ChEi therapy. It is also the first to study the relationship between ACh use and burden in this population with adverse outcomes of longer hospitalization, development of delirium, and change in discharge status from community to an institution.

What can be taken away from this study and added to the literature: ACh are commonly used in hospitalized elderly dementia patients in general (32.7%) and more specifically in those elderly dementia patients who are also concurrently taking ChEi therapy (35.9%). Those on a ChEi are more likely to receive an ACh. The most common ACh prescribed was for the treatment of urinary incontinence, a noted side effect of ChEi therapy. Oxybutynin and tolterodine were the two urinary antispasmodics that were frequently used in this population, accounting for nearly 11% of ACh use. The total number of ACh drugs and the ACh burden were significantly higher in elderly dementia patients on ChEi therapy. Of all ACh drugs given, 39% of them were given as one or two doses and 32% of them were diphenhydramine use, which usually means they were most likely given prophylactically and therefore does not need to be given. Diphenhydramine is routinely given for transfusion prophylaxis without a prior reaction documented. Also, the practice of administering diphenhydramine prophylactically without prior transfusion reaction has no documented benefit and should be avoided.

ACh and ChEi drug use seem to be strongly correlated with each other. There is a significant difference in LOS between those who experience delirium and those that do not ($p<.0001$). There was also a significant difference on where one was discharged to depending on whether or not they experienced delirium ($p<.0001$). Those that did not experience delirium were more likely to be discharge to either community or expired and those that did experience delirium were more likely to be discharged to either an institution

or other. ChEi therapy seems to have an effect on whether a patient experiences delirium and where they are discharged to.

There have been case reports of elderly individuals with a CNS compromising condition treated with oxybutynin (M_1 selective) and tolterodine (non-selective antimuscarinc) developing hallucinations, confusion, and delirium. A preferred treatment option would be an agent that is M_3 specific which have been shown to have no apparent impact on a wide variety of cognitive function tests or to try other methods first. A recent study showed that behavioural strategies (bladder retraining) assisted by biofeedback which has been shown to be more effective and acceptable than oxybutynin treatment in women with urge and mixed incontinence (Burgio et al., 1998).

Behavioral and psychotic symptoms are very common among AD patients and have been reported in more than 80% of subjects in most studies. They are frequently treated with AP, mood stabilizers, and antidepressants (Mega et al., 1996; Stoppe et al., 1999). TCA and AP like olanzapine should be avoided; AP with less ACh activity (e.g. risperidone) may be preferred in a population with dementia (Stoppe et al., 1999).

In addition, cholinesterase inhibitor therapy is associated with significant cost for AD patients. ChEi and ACh drugs have opposing actions, and concomitant use of ACh drugs may therefore reduce the benefits of ChEi therapy. Giving other medications that block or counteract the potential benefits of this therapy make those costs an unnecessary burden on the family and the health care system as a whole.

ACh use does not come without considerable cost to families and the health care system with its associated increased LOS, delirium, risk of being transferred to an

instituition, and mortality. Although some ACh use may be unavoidable in patients with dementia, alternatives with minimal or no ACh activity should be considered first. Careful consideration for potential adverse outcomes in a population that is already at high risk based on age, baseline cognitive impairment, and other medical comorbities needs to be taken into consideration when prescribing drugs for the treatment of some of the conditions that commonly accompany AD.

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APPENDIX A

Defining dementia patients

ICD-9 codes

Disease Category	*Code*	*Diagnosis*
Alzheimer's Disease	331.0	Alzheimer's Disease
Other Dementias	290	Senile and presenile organic psychotic conditions
	290.0	Senile dementia, uncomplicated
	290.1	Presenile dementia
	290.10	Presenile dementia, uncomplicated
	290.11	Presenile dementia with delirium
	290.12	Presenile dementia with delusional features
	290.13	Presenile dementia with depressive features
	290.2	Senile dementia with delusional or depressive features
	290.20	Senile dementia with delusional features
	290.21	Senile dementia with depressive features
	290.3	Senile dementia with delirium
	290.4	Arteriosclerotic dementia
	290.40	Arteriosclerotic dementia, uncomplicated
	290.41	Arteriosclerotic dementia with delirium
	290.42	Arteriosclerotic dementia with delusional features
	290.43	Arteriosclerotic dementia with depressive features
	294.1	Dementia in conditions classified elsewhere
	331.1	Pick's disease
	331.2	Senile degeneration of brain
Delirium	290.11	Presenile dementia with delirium
	290.3	Senile dementia with delirium
	290.41	Atherosclerotic dementia with delirium
	292.81	Drug-induced delirium
	293.0	Acute delirium
	293.1	Subacute delirium

Drugs to treat dementia

Cholinesterase inhibitors:
Donepezil
Rivastigmine
Galantamine
Tacrine

NMDA Antagonists:
Memantine

Appendix B

Centrally-acting drugs with ACh properties

Antihistamines:
Diphenhydramine
Hydroxyzine
Promethazine

Antiparkinson Agents:
Benztropine
Trihexyphenidyl

Antipsychotics:
Chlorpromazine
Clozapine
Olanzapine
Promazine
Thioridazine

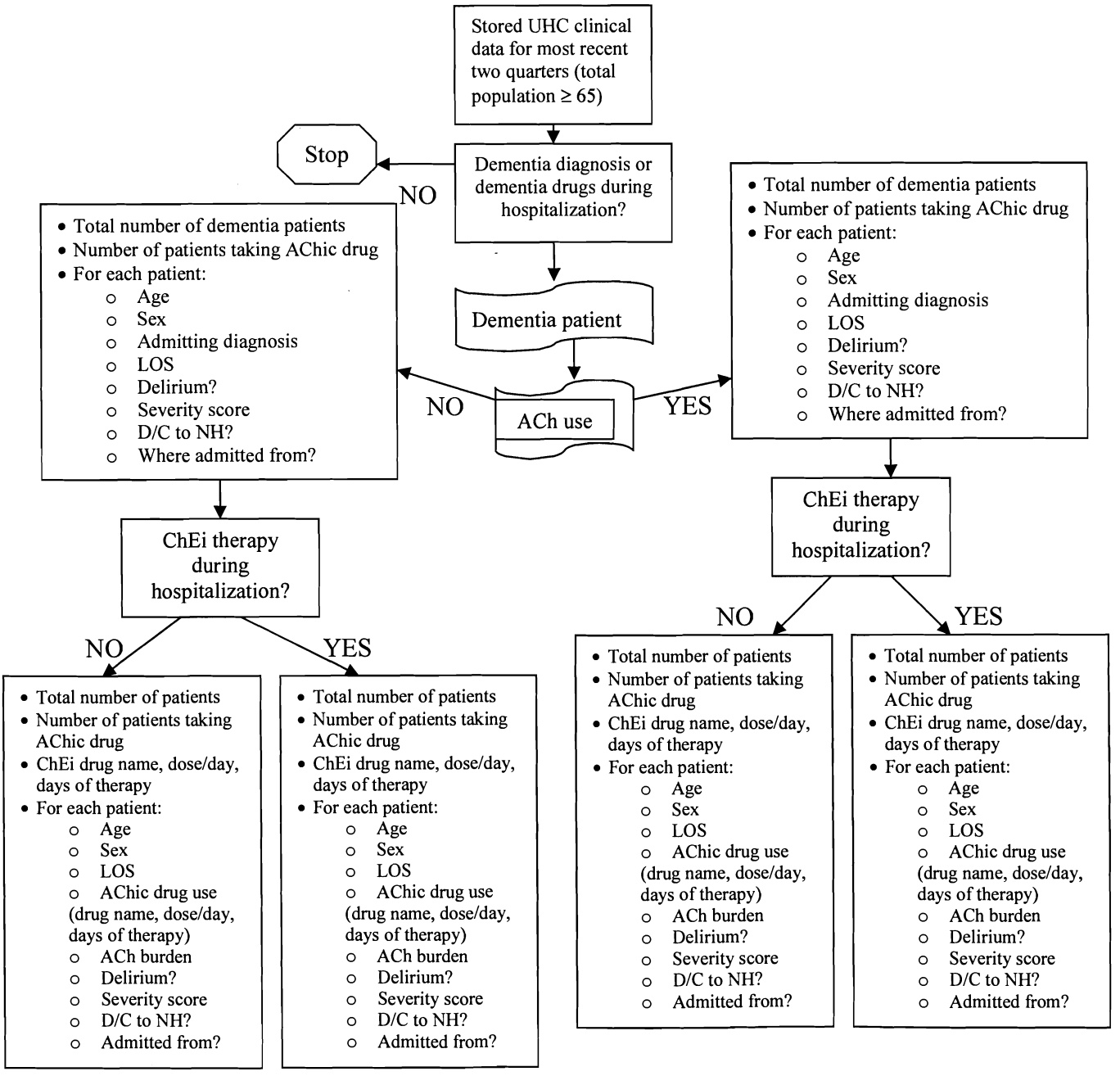
Antispasmotics:
Atropine
Belladonna alkaloids
Belladonna L-alkaloids
Dicyclomine
Dicyclomine/Phenobarbital
Hyoscyamine
Scopolamine

Urinary antispasmodics:
Oxybutynin
Tolterodine

TCA/TCA Combinations:
Amitriptyline
Amitriptyline/chlordiazepoxide
Amitriptyline/perphenazine
Desipramine
Doxepin
Imipramine
Nortriptyline

APPENDIX C

Specific Data Elements



Appendix D

Coding Definitions

No = 1; Yes = 2

Race

1 = White
2 = Black
3 = Asian, Hispanic, Native American/Eskimo, unknown, other

Admission Source

1= Community	2 = Institution	3= Other
Physician referral	SNF (Skilled Nursing Facility)	unknown
Clinic referral	Rehab center	transfer
ER	Psych center	newborn
Home Health referral	Alternative care facility	
Court/Law enforcement	Critical access hospital	
HMO referral	Intermediate care	
From Ambulatory surgery	Short-term acute care	
Routine		

Discharge status

1= Community	2 = Institution	3 = Other	4 = Died
Discharged	Hospic/med facility	Transferred	Expired
Discharged home	LTC hosp	Other	Expired autopsy
Home w/HHC	SNF		Expired no autopsy
Home w/IV	Psych center		
Hospice/home	Rehab center		
Left AMA	Federal hosp		
Other institution for outpatient	ICF		
This institution for outpatien	Acute care facility		

Primary Diagnosis (Based on ICD-9 codes)

Blood d/o (280-289)	DM (250-251)	Respiratory disease/infection (460-519)
Cancer (140-209)	UTI (599)	Respiratory/chest symptoms (786)
Infection (001-139, 440, 785)	Dementia (290-294, 331)	Gastrointestinal disease (520-579)
Injury (830-957, 990-995)	Procedure/aftercare (V50-V59)	Endocrine gland disorders (240-255)
Genitourinary disease (580-629)	Poisoning (960-979)	Mental/mood d/o (290-319)
Malnutrition (260-279, 783)	Fracture (800-829)	Electrolyte/fluid imbalance (276)
Muscularskeletal/connective tissue diseases (710-739)		Skin/subcutaneous tissue disease (680-709)
Symptoms/unk causes of morbity & mortality (799)		Circulatory/vascular/heart disease (390-459)
Signs/Symptoms of ill-defined conditions (780-799)		Complications of medical/surgical care (996-999)
Other (V60-V85, 210-229, 320-324, 742-751, 790)		
Disease of Nervous System (320-389, excluding Alzheimer's Disease)		

APPENDIX E

Anticholinergic Medications: Dose & Potency definitions

Drug #	Drug		Dose			Potency
			1	2	3	
1	amitriptyline	mg	≤25	26 - 149	≥150	3
2	amitriptyline/chlordiazepoxide					3
3	amitriptyline/perphenazine	ea	≤2	>2 - <4	≥4	3
4	atropine (gastrointest)	mg	≤1	>1 - <4	≥4	3
5	atropine sulfate/diphenoxylate	ea	≤2	>2 - <6	≥6	3
6	atropine sulfate/edrophonium chloride					3
7	atropine/hyoscyamine/scopolamine/phenobarbital	ea	≤3	>3 - <8	≥8	3
8	belladonna alkaloids/ergotamine tartrate/phenobarb					3
9	belladonna alkaloids/opium B&O sup	ea	≤1	>1 - <4	≥4	3
10	benztropine	mg	≤1	>1 - <4	≥4	2
11	chlorpromazine	mg	≤50	>50 - <200	≥200	2
12	clozapine	mg	≤25	>25 - <300	≥300	3
13	desipramine	mg	≤25	>25 - <100	≥100	2
14	dicyclomine	mg	≤40	>40 - <80	≥80	3
15	diphenhydramine	mg	≤25	>25 - <100	≥100	3
16	doxepin	mg	≤25	>25 - <50	≥50	3
17	hydroxyzine	mg	≤30	>30 - <75	≥75	2
18	hyoscyamine	mg	≤0.75	>0.75 - <1.5	≥1.5	3
19	hyoscyamine/methenamine mandelate					3
20	imipramine	mg	≤50	>50 - <150	≥150	2
21	nortriptyline	mg	≤25	>25 - <75	≥75	2
22	olanzapine	mg	≤2.5	>2.5 - <10	≥10	2
23	olanzapine/fluoxetine					2
24	oxybutynin	mg	≤5	>5 - <15	≥15	3
25	promazine	mg	≤50	>50 - <200	≥200	3
26	promethazine	mg	≤25	>25 - 100	≥100	3
27	promethazine and combos					3
28	scopolamine (gastrointest)	mg	≤1.2	>1.2 - <2.6	≥2.6	3
29	thioridazine	mg	≤50	>50 - <200	≥200	3
30	tolterodine tartrate	mg	≤2	>2 - 4	>4	2
31	trihexyphenidyl	mg	≤6	>6 - <10	≥10	3

1= Low; 2= Medium; 3= High

VITA

Kelly Jean Gauthier was born in 1978 in Rochester, NY. She received her B.S. degrees in Chemistry and Dance along with minors in biology and math from the State University of New York at Brockport. She is receiving her Pharm.D. and M.S. in pharmacotherapy from VCU School of Pharmacy along with a Certificate in Aging Studies from the Department of Gerontology of VCU and a certificate in Preparing Future Faculty from the Graduate Program of VCU in May 2006. She will be going on to do a primary care pharmacy residency at the VA at Baltimore, MD.

She has been awarded Merck/American Federation for Aging Research (AFAR) Research Scholarship in Geriatric Pharmacology for Medical and Pharmacy Students and Virginia Association on Aging Outstanding Gerontolgy Student Scholarship during her enrollment at VCU. Along with being a member of Student Chapter of the Virginia Society of Health-System Pharmacists, American Pharmacists Association, Virginia Pharmacists Association, and Virginia Academy of Students of Pharmacy.