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Mortality with Alzheimer's Disease Patients with Behaviorial and
Psychological Symptoms of Dementia Taking Atypical
Antipsychotics

by

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DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Nursing

in the

GRADUATE DIVISION

of the

Abstract

Objective: This study examines associations between the use of atypical antipsychotics (AA) and mortality in persons diagnosed with Alzheimer's disease (AD) and behavioral and psychological symptoms of dementia (BPSD).

Background: Data on the use of AAs for behavioral and psychological problems experienced by persons with AD have shown higher risk for mortality, yet continue to be prescribed to ameliorate severe symptoms.

Methods: Retrospectively matched pair case control using a three year survival analysis based on the duration to death from first diagnosis of AD with BPSD for those who were prescribed and not prescribed AAs. Propensity score matching created treatment and case controls based on acuity and estimated probability to use AAs.

Setting: An integrated managed care organization (MCO) consortium in Northern California between the years 2001 and 2008.

Participants: 3,140 AD patients with BPSD, 1,570 AA treatment cases and 1,570 non-AA control cases.

Measurements: Kaplan-Meier and Cox proportional hazards analysis stratified by AA users and non-users.

Results: AA use in AD patients with BPSD is associated with lower risk of death than AA non-use in adjusted models when controlling for congestive heart failure, hypertension, the presence of a pacemaker, acute renal failure and cancer (HR = 0.699, 95% CI = [0.632-0.772], $p < 0.0001$). Patients with a history of using more than one AA over the course of BPSD have lower risk than patients only using one medication (HR = 0.682, 95% CI = [0.59-0.79], p = <.0001). Dosage strength greater than the minimum

strength recommended does not afford higher risk (HR = 1.123, 95% CI = [0.957-1.319], p = 0.1557), non-full compliance is lower risk than full compliance (HR = 0.682, 95% CI = [0.59-0.79], p = <.0001) and one-time prescriptions are higher risk than non-use (HR = 1.428, 95% CI = [1.121-1.818], p = 0.0039).

Conclusions: This study provides evidence that AD patients with BPSD taking AAs have lower risk for death than non-users when controlling for cardiovascular risk factors, pacemakers, renal failure and cancer. The data may suggest mortality risk can be further reduced by careful medication management.

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The Study Problem

Introduction to problem

Atypical antipsychotic (AA) treatment for Alzheimer's disease (AD) patients is common, but remains controversial due to the lack of evidence that atypical antipsychotics (AAs) can both effectively treat psychotic symptoms, often referred to as behavioral and psychological symptoms of dementia (BPSD), and not negatively affect survival rates (L. Schneider, Dagerman, & Insel, 2005). Due to the mortality issues raised by the FDA Health Advisory of 2005 (*FDA Public Health Advisory. Deaths with antipsychotics in elderly patients with behavioral disturbances*, 2005), use of AAs with AD has been limited to the most severe cases and circumstances (Kales et al., 2011). There may be a place for AAs in the range of therapies available if evidence indicated that conditions exist where AAs could be beneficial with lower mortality risk. More research is needed to pinpoint what the most appropriate circumstances are for the use of AAs (Dorsey, Rabbani, Gallagher, Conti, & Alexander, 2010).

Statement of the Problem

To date there is a paucity of knowledge regarding mortality with the use of AAs for AD and BPSD over the long term. Most studies have lasted no longer than three to six months.

Purpose of the Study

This study will provide hazard ratio and probability information on patient mortality with AD diagnoses and the use of AAs for treatment of BPSD over the course of BPSD. This information will demonstrate the risk of death, controlling for use of AAs and common chronic diseases. The target for the information in this study are clinicians

who need risk assessment data in order to make more informed decisions on the prescription of AAs for their patients suffering from AD and BPSD.

Significance

The knowledge to be gained in this study is the finer delineation of what specific dementia subtypes and/or diagnoses, along with possible comorbidities, that have higher risk probabilities related to the use of AAs. Through a better understanding of the risk conditions, better care can be provided to this vulnerable population. The study will inform the healthcare community about AAs with AD and BPSD and the risk of death over a substantially longer period of time than prior studies. In addition, the study may assist geriatric healthcare providers in developing safer clinical protocols for use of AAs with this expanding population.

Research Question

Do mortality rates between atypical antipsychotic users and non-users with Alzheimer's disease and behavioral and psychological symptoms of dementia differ?

Hypothesis

Mortality rates do not differ between atypical antipsychotic users and non-users with Alzheimer's disease and behavioral and psychological symptoms of dementia.

Literature Review

Dementia

Dementia is defined by the American Psychiatric Association in the Diagnostic

and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) manual as a

constellation of cognitive decline symptoms which lead to a significant change in a

person's ability to manage their daily living activities, i.e., activities of daily living

(ADLs) and/or independent activities of daily living (IADLs) ("Diagnostic and statistical

manual of mental disorders," 1994). Dementia is generally a disorder of the elderly. The

incidence of dementia increases with age. Dementia prevalence is estimated to be less

than 0.08% of the under 65 population ("Alzheimer's disease facts and figures," 2010). At

and above age 65, studies have estimated the prevalence of dementia to be between six

and 10 percent of the population (Hendrie, 1998), growing to 40% to 58% for those 85

and older (Ebly, Parhad, Hogan, & Fung, 1994).

Dementia subtypes

Dementia has several subtypes. The most well-known, and most predominant, is

Alzheimer's disease. Other dementia subtypes are vascular dementia, frontotemporal

dementia, Creutzfeld-Jakob dementia and Lewy body disease ("Alzheimer's disease facts

and figures," 2010). Recent research is increasingly indicating that a large percentage of

what was thought to be purely Alzheimer's disease, can be a mix of etiologies, including

Alzheimer's disease, with the most common being mixed dementia (a mix of vascular

dementia and Alzheimer's disease) (Viswanathan, Rocca, & Tzourio, 2009).

Additionally, recent brain pathology studies of those over 65 without dementia have

shown etiologies consistent with of those of Alzheimer's disease and other dementia

subtypes (J. Schneider, Aggarwal, Barnes, Boyle, & Bennett, 2009; J. Schneider, Arvanitakis, Bang, & Bennett, 2007). Consensus around dementia diagnosis is coalescing around the understanding that etiology unto itself is not enough to diagnose dementia. Dementia diagnosis must include abnormal cognitive loss, in addition to etiology ("Alzheimer's disease facts and figures," 2010; Feldman et al., 2008).

Alzheimer's disease

Alzheimer's disease is estimated to be the largest subtype, with a prevalence estimated to be in the range of 47% to 80% of all dementias ("Alzheimer's disease facts and figures," 2010; Feldman et al., 2003; Khan & Alkon, 2010; J. Schneider, et al., 2009). The very wide range of Alzheimer's disease prevalence estimates are in large part due to the difficulty in accurately diagnosing Alzheimer's disease. To date, as it has been the case for several decades, a definitive diagnosis of Alzheimer's disease can only be established post mortem utilizing two elements: first, a clinical diagnosis of abnormal cognitive impairment, and second, autopsy confirmation of the presence of neurofibrillary tangles and amyloid plaques in the brain (Khan & Alkon, 2010). However, there is not a clinical standard for the definition of Alzheimer's disease (Aupperle, 2006). The most widely used research criteria for Alzheimer's disease diagnosis, which is often utilized in a clinical setting, was developed in 1984 by the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association), which is now the Alzheimer's Association (Feldman, et al., 2008).

Vascular dementia

Vascular dementia is due to cerebral vascular issues that affect blood flow to brain cells and negatively affect neuron or brain cell functioning (Chui et al., 1992). The clearest effects of vascular dementia can be evident after cerebral vascular accidents (CVAs), where cognition never recovers or declines after one or more CVAs (Mackowiak-Cordoliani, Bombois, Memin, Hénon, & Pasquier, 2005). Vascular dementia is also sometimes known as multi-infarct dementia (MID), due to the ischemic nature of post-CVA effects (Wiederkehr, Simard, Fortin, & van Reekum, 2008). Vascular dementia can also be due to severe diabetes, where the cerebral vasculature has become compromised by many years of hyperglycemia (Viswanathan, et al., 2009). Vascular dementia is the most prevalent type of dementia in mixed dementia diagnoses (Zekry, Hauw, & Gold, 2002).

Lewy body dementia

Lewy body dementia (LBD) is due to abnormal deposits in the brain, usually near or in the substantia nigra (midbrain), of the protein alpha-synuclein. LBD is characterized by cognitive issues due to the cell degeneration in the substantia nigra pars compacta (Kempster, O'Sullivan, Holton, Revesz, & Lees, 2010). LBD is very similar to Parkinson's disease in its etiology related to substantia nigra cell degeneration, but is not Parkinson's disease. Those with Parkinson disease, however, can progress to LBD in the later stages of Parkinson's (McKeith, 2006).

Frontotemporal dementia

Frontotemporal dementia (FTD), as the name implies, is a dementia which affects cells in the frontotemporal lobe of the brain. Its symptoms include significant changes in

behavior, often socially inappropriate behavior. Pick's disease is also a frontotemporal dementia, because it affects cognition, and is a disease of the frontotemporal lobe (Kertesz, Blair, McMonagle, & Munoz, 2007).

Creutzfeldt-Jakob disease

Creutzfeldt-Jakob disease (CJD is a rare form of dementia. CJD is a brain disease of brain prion protein mis-folding that profoundly affects cognition and behavior. It is typically met with a quick onset and mortality within 1 to 2 years (Van Everbroeck et al., 2004).

Mixed dementia

Mixed dementia generally presents with the standard symptoms of Alzheimer's disease, but will also be symptomatic of other dementias, most often vascular dementia ("Alzheimer's disease facts and figures," 2010). The DSM-IV defines mixed dementia as being a combination of Alzheimer's disease and vascular dementia ("Diagnostic and statistical manual of mental disorders," 1994). However, studies have shown LBD and FTD have been present with Alzheimer's disease in a mixed dementia mode (Kertesz, et al., 2007; J. Schneider, et al., 2007). All the dementia diagnoses with brain cell degeneration, Alzheimer's disease, FTD, CJD and LBD share that common trait of cell transformation. There is no ICD-9 or ICD-10 code for mixed dementia (Langa, Foster, & Larson, 2004). At a clinical level, mixed dementia is identified with the two diagnostic codes for Alzheimer's disease and vascular dementia.

Other dementia diagnoses and precursors

Diagnosis of the various dementia subtypes is very difficult and not 100% accurate. There is currently no accurate biomarker for any of the dementias while patients

are living (Dubois et al., 2007). Furthermore, there is debate as to whether post expiration autopsies of brain material, the current standard for accurate diagnosis of Alzheimer's disease, as an example, can on their own provide 100% accurate diagnosis of Alzheimer's disease on its own (Khan & Alkon, 2010). Because of this, at a clinical level, two diagnoses were developed to fill in uncertainty where it is believed a condition and/or pre-condition of dementia exists, but which does not meet the specific etiology criteria for other dementia subtypes. Those diagnoses are dementia unspecified and mild cognitive impairment.

    Dementia unspecified

       Dementia unspecified is a diagnosis of exclusion. Patients with dementia unspecified exhibit definite memory loss, as designated by one of the cognitive screening tests, such as the Mini-Mental Status Exam (MMSE). However, there is not a clear etiology based on tests to categorize the dementia as one of the more specific dementia types, especially in the early stages, such as Alzheimer's disease or vascular dementia (Feldman, et al., 2008).

       The DSM-IV categorizes non-specific dementia into four subtypes, uncomplicated, with delirium, with delusions, and with depression and with behavioral disturbances. The last three, delusions, depression and behavioral disturbances are all a part of the BPSD definition. All of these non-specific dementia diagnoses have their own International Statistical Classification of Diseases and Related Health Problems (ICD) diagnoses codes, which were purposely designed to follow the DSM manuals.

Mild cognitive impairment

Mild cognitive impairment (MCI) is not considered a subtype of dementia, but a large number of patients with MCI go on to dementia. MCI represents, in some people, the very earlier stages of dementia, often presenting with minor memory loss, but not functional loss. Memory loss normally occurs as people age and a number of cognitive and neuropsychiatric tests establish norms based on age. MCI is considered abnormal memory loss, but not at the threshold of a categorization of dementia (Chertkow et al., 2008). About 50% of the people who are first diagnosed with MCI will go on to dementia. MCI is often given as an initial diagnosis to allow more time to test for etiology or medication use that may degrade cognition but not qualify as dementia (D. Chapman, Williams, Strine, Anda, & Moore, 2006). Many times, MCI is diagnosed when cognitive test scores are at the very low end of the normal range.

Behavioral and Psychological Symptoms of Dementia (BPSD)

Behavioral and psychological symptoms (BPS), as a distinct acronym from BPSD, are also referred to as neuropsychiatric symptoms in the psychiatric and neurology fields. Neuropsychiatric symptoms include depression, apathy and psychosis, with psychosis symptoms further subdivided into hallucination, delusions and sometimes aggression as defined by the DSM-IV. The use of the term and acronym BPSD became widespread in the late 1990s and early 2000s within the dementia and pharmaceutical research community after the 1996 International Consensus Conference on Behavioral and Disturbances of Dementia issued the conference paper: "Report on the International Consensus Conference on Behavioral Disturbances of Dementia" (Jeste, Meeks, Kim, & Zubenko, 2006). The report defined BPSD as disruptive behavioral problems, psychosis,

wandering, apathy, severe depression, agitation, aggression, hallucinations and delusions. These symptoms are very close to and consistent with the criteria of neuropsychiatric symptoms defined by the DSM-IV (Finkel, de Silva, Cohen, Miller, & Sartorious, 1996).

The genesis of the 1996 conference was not due to BPSD being a new phenomenon, but because AAs, which had come into the market in the early 1990s for treatment with schizophrenia, had grown in widespread use for BPSD based on the positive results of an increasing number of drug research trials of AAs with BPSD (Laughren, 2001). The dementia clinical and research community needed to develop an operational definition for BPSD (Finkel, et al., 1996). The BPSD acronym was used most widely by the pharmaceutical industry to help coalesce funding of AA research around the use within dementia population (Laughren, 2001).

However, neuropsychiatric symptoms are not disease specific and can be found outside of dementia and psychotic conditions, e.g., schizophrenia (Assal & Cummings, 2002). One study, The Aging, Demographics and Memory Study (ADAMS), consisting of a cohort of 856 subjects over 71 years of age, found that 17.7% of the normal cognition group had at least one incident of a neuropsychiatric symptom over a two year period.

Behavioral and psychological symptom prevalence & incidence

Utilizing neuropsychiatric symptom and cognitive instruments, only a few researchers have attempted to identify the incidence of individual BPS subtypes. The following is a review of studies that have estimated the incidence of BPS subtypes with varying results. Most are consistent with the finding that agitation and apathy have the highest incidence. However, the incidence of agitation was the highest BPS subtype for a

few studies. Agitation occurs in more than 80% of Alzheimer's disease patients according to a review of several studies by Jeste et al (2006). The German study previously mentioned, using the BEHAVE-AD rating scale that showed 100% of the study subjects experienced an agitation episode (Haupt, Kurz, & Jänner, 2000). A four year longitudinal United Kingdom study of 410 Alzheimer's disease clinic patients identified aggression as having the highest BPSD incidence at a 4.17 relative risk (CI: 2.67-6.50) followed by hallucinations/delusions, then depression/apathy (Gilley et al., 2004).

However, other studies using the Neuropsychiatric Inventory (NPI) rating scale have shown apathy to have the highest incidence. In the UCLA study, the percent of patients experiencing NPI disturbances at least once were: apathy 72%, agitation 60%, anxiety 48%, irritability 42%, dysphoria 38%, and aberrant motor behavior 38%, disinhibition 36%, delusions 22%, and hallucinations 10% (Mega, Cummings, Fiorello, & Gornbein, 1996). In the European Alzheimer's Disease Consortium (EADC) study, NPI testing showed the following incidences: apathy 59.6%, depression 58.5%, irritability 44.6%, anxiety 44% and agitation 41.5% (Petrovic et al., 2007).

Finally, a review of three European studies generated a mean across the three studies using NPI disturbances, with apathy also having the highest incidence: apathy 55.5%, depression 44.9%, irritability 30.6%, anxiety 42.0%, agitation 35.0%, aberrant motor behavior 24.7% and delusions 22.0% (Robert et al., 2005).

BPSD Etiology

A few studies have been executed with the goal of identifying the etiology of BPSD. The etiology of dementia is generally unknown outside of what's known about the

condition of the brain on autopsy for conditions such as Alzheimer's disease, vascular dementia, FTD, CJD and LBD (Barnes et al., 2005; Dubois, et al., 2007; Tarawneh & Holtzman, 2009). However, the causes of those dementias are unknown. The same holds true for BPSD. A number of studies have investigated genetic sources of BPSD. Several studies and literature reviews of genetic risk factors for BPSD have not been able to find any significance between genetic markers and BPSD (Borroni, Costanzi, & Padovani, 2010; Engelborghs et al., 2006; McIlroy & Craig, 2004; Pritchard et al., 2007). Another set of studies have investigated brain activity through magnetic resonance imaging (MRI) and positron emission tomography (PET) with BPSD. To date, however, none have found any significant brain activity etiologies directly associated with BPSD (Khan & Alkon, 2010; Petersen & Trojanowski, 2009; Rockwood, 2010).

Mortality associated with BPSD

What is the mortality associated with BPSD not taking into consideration medication use? Only one study of BPSD patients investigated the cause of death. The study is an 11-year prospective longitudinal study of BPSD patients in the United Kingdom. Cause of death was recorded from death certificates, and when possible, post mortem autopsies. It indicated pneumonia was the cause of death in the majority of cases, 57%, followed by cardiovascular disease, 16%, and pulmonary embolus, 14%. Dementia was mentioned on the death certificates in 73% of the cases, with 58% debilitated by the dementia in one form or another, and 76% in an institution for an average of 18 months at the time of death (Keene, Hope, Fairburn, & Jacoby, 2001).

BPSD treatment options

A number of studies have looked at the issue of how to effectively treat BPSD. The studies generally break down between non-pharmaceutical treatment and pharmaceutical treatment. As previously stated, research has shown that BPSD and cognition dysfunction are separate etiologies and should generally be treated differently. The discussion below will focus primarily on BPSD treatments. However, it will also include a review of studies that looked at cognition improvement strategies as treatments for BPSD and examine why they failed to treat severe cases of BPSD.

Non-pharmaceutical treatment

There has generally been a consensus that non-pharmaceutical treatments should be attempted first in all cases. Pharmaceuticals, in particular antipsychotics, should be utilized only as a last resort, only in moderate to severe cases of BPSD and only after careful analysis and trial in each case (Finkel, et al., 1996; Herrmann & Gauthier, 2008; Hogan et al., 2008; Salzman et al., 2008). The non-pharmaceutical interventions which showed some significance in ameliorating BPSD include exercise programs, unmet needs analysis and treatments, caregiver training, environmental changes and bright light therapy (Ayalon, Gum, Feliciano, & Arean, 2006; Livingston, Johnston, Katona, Paton, & Lyketsos, 2005). However, if non-pharmaceutical interventions fail to relieve the BPSD, such that the patient is in significant distress and/or is a significant or undue burden to their caregivers and healthcare providers, then pharmaceuticals should be seriously considered (Assal & van der Meulen, 2009; Gauthier et al., 2010; Jeste et al., 2007; Kirshner, 2008; Okura et al., 2010; Salzman, et al., 2008). The pharmaceutical

class that has been shown to most effectively relieve BPSD, or provide partial relief for it, is antipsychotics.

Pharmaceutical Treatment - Antipsychotics

Antipsychotic medications, also known as neuroleptics, have been shown to be efficacious in treatment of psychosis and behavioral problems for decades (Keltner & Folks, 2005). Neuroleptics are subdivided into two groups, typical and atypical antipsychotics.

Typical antipsychotics

Typical antipsychotics, also referred to as conventional antipsychotics or first generation antipsychotics, were developed in the 1950s primarily for psychosis symptoms of schizophrenics. Typical antipsychotics have also found some application in cases of delirium, delusions and mania (Healy, 2004). There are more than two typical antipsychotics in use today, but only two will be discussed in brief detail. The two typical antipsychotics to be discussed below are used today in acute BPSD situations in limited circumstances.

One of the early typical antipsychotics was chlorpromazine, or the trade name Thorazine. It is still used today as therapy for psychosis. In the central nervous system, chlorpromazine affects a wide variety of receptors, primarily dopamine receptors, but also cholinergic, adrenergic and histamine receptors. The broad effects of chlorpromazine, while an advantage in many cases, limits its broader use as antipsychotic therapy. The most serious group of side effects is extrapyramidal side effects (EPS), including tardive dyskinesia (Healy, 2004).

Another older typical antipsychotic in wide use for acute and severe psychosis (including BPSD) is haloperidol, also known under the trade name Haldol. It is an injectable medication, whose therapeutic levels can last for weeks (Keltner & Folks, 2005). Haloperidol is most often used in severe psychosis situations to treat acute and severe aggression in dementia patients, where the evidence indicates it has some efficacy (Lonergan, Luxenberg, Colford John, & Birks, 2002). Haloperidol treatment is often due to non-compliance with already prescribed antipsychotic medications to treat a history of psychosis. It is largely used in single event situations and not continuously because of the significant side effects if used continuously. One such side effect is EPS (Hughes & Kleespies, 2003).

Atypical antipsychotics

The newer antipsychotic class of neuroleptics, AAs, is also referred to as second generation antipsychotics. AAs began to appear in the late 1980s, with the first being clozapine (Clozaril). Clozapine was found to be effective in only a third of patients with psychosis, in particular schizophrenia, and usage required frequent and expensive blood tests to monitor for toxic levels of the medication. However, in the early 1990s', newer AAs became available that did not share the toxicity of clozapine. These newer AAs were preferred over the typical antipsychotics because they affected fewer receptors, while keeping the primary effect on dopamine receptors, and did not share the EPS of the conventional antipsychotics (Keltner & Folks, 2005). The three major AAs that were the most widely used for BPSD, and appear in most of the research literature on the use of AAs with BPSD, will be briefly reviewed below.

The most widely used AA for BPSD is risperidone, under the trade name Risperdal. Risperidone, approved by the FDA in 1993, had the distinction of also being approved for use with adolescents, 13-17 years old, for schizophrenia. It was later approved for use with psychosis in conjunction with bipolar disorder. Risperidone use with teens was significant, as schizophrenia generally becomes symptomatic in the late teens. However, it was in 1993 that risperidone also began to be used for psychosis with dementia patients. The first study involving risperidone and dementia appeared in 1995 (Shen, 1999).

Olanzapine, was approved by the FDA in 1996 for use with psychosis in schizophrenia and bipolar disorder, and is distributed under the trade name Zyprexa in the United States. Olanzapine is slightly different from risperidone because it has a greater affinity to serotonin receptors than dopamine receptors. The first study of olanzapine and BPSD appeared in 1997 (Shen, 1999).

Quetiapine was approved by the FDA in 1997 for use with psychosis in schizophrenia, in addition to bipolar mania and depression. It is distributed under the trade name Seroquel in the United States. The first study of quetiapine and BPSD also appeared in 1997. Like olanzapine, quetiapine has a stronger affinity to serotonin than it does to dopamine receptors.

Atypical antipsychotic treatment efficacy for BPSD

While there are a large number of studies looking at the efficacy of AAs with non-dementia psychosis, there are only a moderate number of studies looking at the efficacy of AAs with BPSD. Of these AA BPSD studies, a much smaller subset has investigated mortality as an outcome in the analysis, and generally one of several

outcomes. A very small number of studies research mortality as the only outcome. An even smaller number of studies analyze mortality over a number of years.

The following discussion will briefly review what studies have been completed on the efficacy of AAs with patients with BPSD, with Alzheimer's disease and those with non-Alzheimer's disease dementia. The literature review of the efficacy of AAs with BPSD needs to be framed in terms of a seminal event, the FDA Public Health Advisory of 2005 (*FDA Public Health Advisory. Deaths with antipsychotics in elderly patients with behavioral disturbances*, 2005). The literature needs to be viewed within the timeframe of pre-2005 and post-2005, as the studies published during the post-2005 timeframe reflect the context of that advisory. Most of the efficacy studies were executed prior to the advisory. After the advisory the number of studies focusing on mortality increased dramatically (Dorsey, et al., 2010).

Efficacy emphasis - pre-2005 FDA Health Advisory

A large number of studies used patients with all subtypes of BPSD when investigating the efficacy of AAs with BPSD. This was particularly true in the 5 to 7 year period prior to the 2005 FDA Health Advisory (FDAHA) on use of AAs with BPSD (Suh, 2009). In light of scant evidence to hypothesize otherwise, many investigators posited BPSD as being very similar to neuropsychiatric issues and behavior problems of schizophrenics given the symptoms were very similar (Jeste, Dolder, Nayak, & Salzman, 2005). Some of the drug efficacy studies from this period did show some positive efficacy, however, these studies were largely limited to the two AAs risperidone and olanzapine specifically (Sink, Holden, & Yaffe, 2005).

There were five heavily cited RCT studies published between 1999 and 2003, all double blinded RCT placebo versus one or more AAs, that all found significant results in efficacy for the AAs risperidone and olanzapine. The majority of patients in these five studies were Alzheimer's disease patients, but only one of the studies had 100% of the patients with Alzheimer's disease. The remainder of the studies had a varying prevalence of patients with vascular dementia and mixed dementia. All studies lasted from six to 12 weeks and used the Behavioral Pathology in Alzheimer's disease (BEHAVE-AD) (2), NPI (1) and the Cohen-Mansfield Agitation Inventory (CMAI) (2) instruments to measure changes in BPSD. The two studies measuring risperidone versus placebo achieved reductions in BEHAVE-AD scores with insignificant differences in side effects (outside of slight EPS for the drug group) or adverse effects between drug and placebo (De Deyn et al., 1999; Katz et al., 1999). The study investigating olanzapine versus placebo recorded a significant reduction in NPI scores (Street et al., 2000). The study comparing risperidone to placebo and haloperidol found low dose risperidone decreased the severity and frequency of BPSD as measured by the CMAI and BEHAVE-AD instruments (Chan et al., 2001). The fifth study of risperidone versus placebo found decreases in CMAI total scores for risperidone (Brodaty et al., 2003).

There were, however, a few RCT studies that found the efficacy of the AAs to be much more moderate (Carson, McDonagh, & Peterson, 2006; L. Schneider, et al., 2005; Sink, et al., 2005). While there is heavy reference to RCTs in the literature that showed higher than expected mortality and adverse side effects that served as the foundation for the 2005 FDAHA on AAs and BPSD, these RCTs are only available in poster form. None of them have been published. They were either posters, conference papers or drug

manufacturer RCT reports only available to the FDA (Carson, et al., 2006) and selected researchers with funding from the pharmaceutical companies with interests in the medications under research.

FDA Health Advisory – April 2005

The FDA approved application of antipsychotics for severe forms of psychosis, such as schizophrenia as documented previously in the mid to late 1990s, but never for dementia. However, AA treatment for dementia patients became wide spread very soon after they were approved for schizophrenia during the years 1993 to 1997 (L. Schneider, et al., 2005). In its April 2005 Public Health Advisory titled "Public Health Advisory: Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances", the FDA stated that use of antipsychotics were off-label (*FDA Public Health Advisory. Deaths with antipsychotics in elderly patients with behavioral disturbances*, 2005). The reason given for the off label use advisory was increased mortality associated with AAs based on a review of studies from the prior several years. Therefore, the FDA mandated black box warnings for dementia patients with BPSD using AAs. (*FDA Public Health Advisory. Deaths with antipsychotics in elderly patients with behavioral disturbances*, 2005)

The FDA stated that increased mortality is associated with AAs in 15 of 17 placebo controlled trials involving 5,106 patients. The odds ratios of death were in some cases 1.16 to 1.17 in analyses of several of the studies. The FDA named four AAs used with dementia patients with BPSD as being a part of those trials: olanzapine, risperidone, quetiapine and aripiprazole. All of the medications named share a similar chemical structure. Therefore, the FDA included two additional medications, clozapine and ziprasidone, that were not part of the original 17 studies reviewed, because they shared

the same chemical structure as the four AAs named in the advisory. The increased

mortality, according to the FDAHA, was due to heart related events, mostly

cerebrovascular adverse events (CVAE), and infections, primarily pneumonia. The black

box warnings for AAs being used by dementia patients with BPSD explicitly state that

CVAEs are a side effect of using AAs (*FDA Public Health Advisory. Deaths with

antipsychotics in elderly patients with behavioral disturbances*, 2005).

Post-2005 FDA Health Advisory

 Use of atypical antipsychotics

  Because there are no FDA approved medications to treat BPSD unresponsive to

non-pharmaceutical approaches, off-label usage of antipsychotics continues for BPSD

patients (Kirshner, 2008). A study of AA prescriptions, for all uses for all types of

patients, between January 2003 and December 2008, found that AA prescriptions for

dementia patients greater than 65 year old decreased 18.5% annually between May 2005

and December 2008. The FDAHA for AAs and dementia was issued in April 2005. Prior

to issuance of the FDAHA, between January 2003 and March 2005, AA prescriptions for

dementia patients greater than 65 had grown by 16%. The number of patients over 65

with dementia taking AAs had declined from 590,000 in 2003 to 400,000 in 2008, 3 ½

years after the health advisory (Dorsey, et al., 2010). However, 400,000 dementia patients

continuing to take AAs represents high usage incidence.

 Mortality, co-morbidity and BPSD emphasis

  After the issuance of the 2005 FDAHA, there was a marked shift in the studies

published involving BPSD with AAs. There were essentially six areas of focus of the

post-FDAHA literature, which had not already been in the research pipeline prior to the

FDAHA: 1. White papers and clinical guidance papers on how to adjust clinical treatment of BPSD patients in light of the FDAHA and black box warning on AAs with BPSD (Assal & van der Meulen, 2009; C. Ballard, Corbett, Chitramohan, & Aarsland, 2009; Bianchetti, Ranieri, Margiotta, & Trabucchi, 2006; Feldman, et al., 2008; Fillit et al., 2006; Gauthier, et al., 2010; Herrmann & Gauthier, 2008; Jeste, et al., 2006; Meeks, 2008; Salzman, et al., 2008). 2. Critiques of the FDAHA and black box warning, with suggestions of directions where future research should concentrate in light of the FDAHA (Dorsey, et al., 2010; Jeste, et al., 2007; Suh, 2009). 3. RCTs and other studies that concentrated on the two AAs, risperidone and olanzapine, which showed some efficacy in the pre-FDAHA period with modified dosing and duration parameters (Angelini, Bendini, Neviani, & Neri, 2007; Kirbach, Simpson, Nietert, & Mintzer, 2008; Liperoti et al., 2009; Lövheim, Sandman, Kallin, Karlsson, & Gustafson, 2006; Mintzer et al., 2006; Suh & Shah, 2005; Sultzer et al., 2008). 4. Studies focused on non-pharmaceutical treatments for severe cases of BPSD (Ayalon, et al., 2006; Gauthier, et al., 2010; Gitlin, Winter, Dennis, & Hauck, 2007; Hogan, et al., 2008). 5. Studies more finely focused on dementia subtypes and co-morbidities because of the morbidity issues raised as part of the health advisory. 6. Studies more focused on the etiology of mortality issues by developing and analyzing more longitudinal timeframes. Because of the focus of this study, mortality with AD patients with BPSD, the following will be a more detailed review and discussion of studies in five and six above, mortality and morbidity..

Associations between morbidity and mortality in BPSD patients had been analyzed in very few studies, even after the FDAHA. There have been opinion papers that have speculated on the findings of the FDA in the FDAHA (Snowdon, 2006;

Viswanathan, et al., 2009). Viswanathan et al (2009) speculated that the CVAE issues were related to documented arrhythmia issues with antipsychotics as a class of medications. In the discussion section, Viswanathan et al (2009) gave a blueprint for a study to look at the relationship among previous CVAE comorbidities, AA usage and a BPSD condition. But there have been very few studies yet published that have analyzed a possible association. There was one retrospective study published post FDAHA that did look at cerebrovascular accidents as a pre-condition and its possible association with mortality with patients with Alzheimer's disease using AAs, but found no association. However it did not include BPSD as a inclusionary criteria (Helzner et al., 2008).

Another post-FDAHA study analyzed mortality between atypical and conventional antipsychotic users with BPSD, where a cardio/cerebrovascular pre-condition was a possible covariate. In Liperoti et al (2009), a cohort longitudinal study of 9,729 nursing home patients with dementia taking antipsychotics living in 1,581 Medicare or Medicaid certified nursing homes in five U.S. states, was analyzed for mortality rates during a two-year period 1998 to 2000. Among this population of dementia patients using antipsychotics, 67% were taking an AA. Of these AA users, 36% had been diagnosed with Alzheimer's disease, while the remaining 64% patients had been diagnosed with other forms of dementia. The dementia types were unspecified in the published paper. BPSD subtypes were broken out in the sample tables, with depression having the highest share of patients, 48.7%, inappropriate behavior, 39.7%, verbal aggression, 34.3%, physical aggression, 25.9%, and with the remainder of the BPSD subtypes below, 20%. The subgroup of AA users had a cardio/cerebrovascular prevalence of 75.3%. The study found no significant association between a cardio/cerebrovascular

status and mortality. The association between mortality and the different BPSD subtypes was not included.

Unfortunately, the Liperoti et al (2009) study did not break out cerebrovascular status from cardiovascular. Within the study's discussion section, it did recognize this was a shortcoming of the study in light of the CVAE issues disclosed in the FDAHA. While this study does not have the deficiencies of prior BPSD studies of short timeframe and small sample size, it does not provide the insight into significance of CVAE as a precondition for higher mortality in associated use of AAs. Nor did it provide any insight into the relationship of BPSD subtypes with mortality. However, the study's goal was to analyze the differences in mortality between atypical and antipsychotic users and it provided an excellent analysis of the different associations.

The study that comes closest to providing the best understanding of the relationship of mortality with BPSD patients taking AAs, while at the same time controlling for co-morbidities, is "Antipsychotic Drug Use and Mortality in Older Adults with Dementia" (Gill et al., 2007). This is a population based retrospective cohort study that utilizes 27,259 matched pairs of dementia patients taking atypical or conventional antipsychotics over the period between April 1997 and March 2002. The sample incorporated both community dwelling and long-term care residents in the Ontario province of Canada. Because Canada has a single-payer government run health care system, clinical and pharmaceutical dispensing records were readily available for analysis. Time periods for death were tracked at 30, 60, 120 and 180 days after first dispensing of the AAs medications risperidone, olanzapine and quetiapine; and the typical antipsychotics haloperidol, chlorpromazine, trifluoperazine, fluphenazine,

flupenthixol, perphenazine, loxapine, pericyazine, pimozide and thioridazine. Results were compared with match paired dementia patients not taking any neuroleptic in the cohort with the non-antipsychotic group. The non-antipsychotic patients were pair matched with the antipsychotic patients using propensity scores based on 42 covariates, which included age, gender, income status, medical history (15 covariates), markers of dementia severity (4 covariates), other medications (4 covariates) and mean number of medical contacts (4 covariates). Results of the Gill et al (2007) study indicate there is a 31 percent higher risk for death for AA users over non-AA users with community dwelling dementia patients. These results are relatively consistent with RCTs of similar group comparisons of AA users over non-AA users (Jeste, et al., 2005; L. Schneider, et al., 2005; Wang et al., 2005). Most all of these studies were published before or close to the FDAHA.

The strengths of the Gill et al (2007) study are in its sample size, the propensity matching system and the number of significant covariates. In regards to the sample size, the study is the largest of any of the observational studies related to the AAs and dementia, and certainly far larger than any of the meta-analyses of RCTs reviewed. The large sample size also allowed the authors to analyze smaller sub-segments, such as individual medications and community versus long-term care, without losing significance. The paired matching system facilitated significantly reduced possible confounding factors in the analyses. Because the study was not a RCT and subjects were not randomly assigned to medication and non-medication groups, the potential for confounding factors could still be high, although the use of a paired matching system, while not eliminating the issue of confounding factors, helped to reduce it. The study also

included over 40 covariates, 15 of which were related to medical history. Those covariates were key in establishing the paired subject matches.

The study did not take advantage of the large sample size to study individual co-morbidities, such as cerebrovascular disease, and their relationship to mortality. Cerebrovascular disease accounted for 27.7%, of the antipsychotic group and 31.7% of the non-antipsychotic group. This type of study needs sufficient sample size to test for cerebrovascular disease as a predictor variable. One of the reasons earlier studies have been unable to test for significance of co-morbidities against mortality is due to their small overall samples, which would have left sub-segments, such as type of dementia and multiple medications, too small to measure with any significance. A key criticism of the study is that it is observational. Therefore, it doesn't have the cause and effect strength of RCT. Another weakness of the study is in relationship to the focus of this literature review. The study didn't delineate by BPSD subtypes or subgroups. The study chose to delineate subjects by four of what they called "markers of dementia severity" (Gill, et al., 2007). These markers were: urinary continence, fecal incontinence, hospitalization falls in the past year and hospitalization with delirium in the past year. However, there was no detail on these dementia severity markers as to why they were chosen or which marker or set of markers identified specific levels of severity.

The Gill et al (2007) study comes closest to the current study in its overall design and objectives. It is the goal of this study to take the Gill et al (2007) study as a model and to go to a deeper level by analyzing the association between mortality and AA usage of AD patients with BPSD rather than by all dementias.

To summarize the gaps in the literature on AAs and mortality with AD patients with BPSD: first, most literature to date investigates this issue over short term periods, from 30 to 180 days. There are very few studies longer term that look at AA usage over 1 year and more. Second, most all of the studies have not investigated AD with BPSD specifically as a criteria for entry into the study. Third, most all studies are safety and efficacy studies on AA usage and start from AA treatment. They do not investigate AA use within context of the entire course of AD with BPSD as a disease state.

Theory

The goal of this study is to provide evidence-based insight on the incidence of death in AD patients with BPSD taking AAs. One of the objectives of the study is to develop significant probability profiles to be used with decision models for the medical decision making process to determine which clinical circumstances may or not be appropriate for the use of antipsychotics with AD and BPSD sequelae. Therefore, a theoretical foundation of this study is based on medical decision theory. This is accomplished by parsing out statistically significant conditions and circumstances where death is more likely and not likely. The core of the study is a probabilistic analysis of the risks involved in utilizing AAs for AD with BPSD. The theoretical basis for this approach is set in medical decision making theory. The value in evidence-based medical decision making is supported by decision models where conditional probabilities form the core of the decision analysis.

Theoretical Background on Medical Decision Making

Medical practice involves a great deal of uncertainty (Gillett, 2004; R. M. Kaplan, Ganiats, & Frosch, 2004; Scheidt, Wenger, & M., 2004). Every patient's physiological condition involves a great deal of complexity, in particular with elderly patients, where multiple co-morbidities and medications can confound condition assessment and treatment (Park-Wyllie et al., 2009). Many conditions, in particular dementia, are only partially understood in terms of pathophysiology and disease course ("Alzheimer's disease facts and figures," 2010). When adding other dimensions into the patient's overall medical condition, such as patient and family wishes, as well as available health care

resources to treat various conditions, accurately assessing the patient's condition and risks for various treatments can become cumbersome.

Heuristic decision making, sometimes referred to as ad hoc decision making, has represented the most common decision making process in medicine prior to the explosion in research in the modern medical era, and remains today as a key component in medical decision making (G. B. Chapman & Sonnenberg, 2000). Ad hoc decision making represents the judgments of clinicians about appropriate care for individual patient cases. It is based on the clinician training, experience, interpretation of past evidence and the practice of the institution where care is provided by the clinician (G. B. Chapman & Sonnenberg, 2000). Ad Hoc had been the dominant component in medical decision making heretofore, and often continues to be the dominant component. Its weakness is health care provider bias, most often judgment bias. Both ad hoc decision making and bias are represented in The Medical Decision Making Model, as shown in Figure 2.

The expanding importance and weight of the medical research over the ad hoc effect on medical decisions is in large part due to its impact on decreasing bias in medical decision making (R. M. Kaplan & Frosch, 2005). The effect of bias has been well documented in medical decision making (Loewenstein, 2005). As an example, physicians, even when analyzing the same clinical information, will disagree with each other. One study on vascular stenosis, where accurate estimates of the size of the stenosis are central to treatment, found physicians disagreeing significantly on stenosis estimates based on CT imaging in 60% of the cases (Zir, Miller, Dinsmore, Gilbert, & Harthorne, 1976). Furthermore, physicians have been found to disagree with their own first judgment in as much as a third of their cases (Eddy, 1994). However, medical research and the use

of evidence based practice processes, discussed in more detail below, has been shown to significantly decrease judgment bias (R. M. Kaplan & Frosch, 2005).

By objectively establishing the probability and risk of each component of the patient's condition and treatment risks, both patient and care provider can more thoughtfully decide on the best course of action for treatment over time (Lurie & Sox, 1999; Ratliff, Angell, Dow, Kuppermann, & Nease, 1999). The objective of medical decision making theory and practice is, ideally, to provide a more objective evidence-based framework and basis for each component of the process.

A number of studies on the use of AAs by AD patients with BPSD have established a significant association between use and higher death rates (Kryzhanovskaya et al., 2006; L. Schneider, et al., 2005; Wang, et al., 2005). It is the objective of this study to investigate if there are conditions which indicate lower death rate associations and to generate probabilities for those associations which can be utilized by healthcare providers in making decisions about whether to prescribe AAs and to whom. Medical decision making theory provides a framework via various evidence based decision algorithms, which can incorporate those probabilities, to help health care providers, patients, family and designated decision makers with the difficult task of choosing the appropriate treatment. In the case of this study, the objective is to aid in the decision to choose a medication treatment or non-medication treatment and for whom.

Medical Decision Making Theory

Introduction to evidence-based practice

Medical decision making theory is a subset of evidence-based practice (EBP) methodologies. EBP is the utilization of the best and most current medical research in

making decisions about the care of patients (Sackett, Rosenberg, Gray, Haynes, &

Richardson, 1996). EBP is a stepwise process that continuously synthesizes information

on the patient and best medical research evidence for patient care. As depicted in Figure

1, EBP is circular in nature, following these steps: 1. Evaluation of the patient. 2. Best

medical research evidence acquired. 3. Critical appraisal of the evidence. 4. Evidence

applied. 5. Patient outcome(s) analyzed, including patient input. 6. Treatment(s) adjusted.

("Council for training in evidence-based behavioral practice. definition and competencies

for evidence-based behavioral practice (EBBP)," 2011). These steps can be summarized

as a continuous process of evaluation, evidence incorporation into healthcare decisions,

and then the re-evaluation of those decisions.

Figure 1

Evidence-based Practice Stepwise Pathway
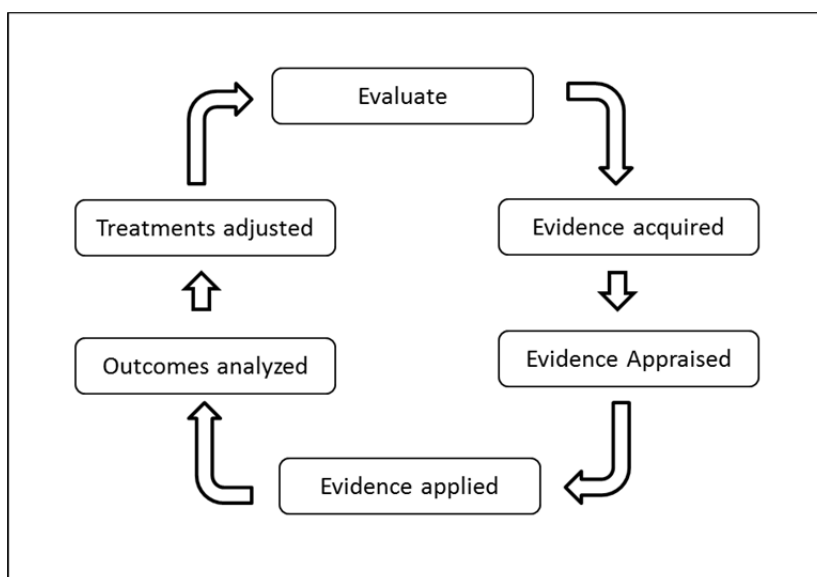
The EBP process repeats itself until patient goals and objectives are met. The

repetitive, but evolutionary, nature of EBP is due to the fact that as time passes more is

learned about a patient's condition through diagnostics and treatment. Patient conditions

can also change in response to a patient's experience and thinking about treatment, as well as in response to a patient's family's experience and thinking. Furthermore, medical resources and costs can become a factor in the medical decision making. All of these elements are factors in the medical decision making process as the EBP pathway repeats itself.

The medical research pathway

The process of medical decision making goes beyond the best current medical research and encompasses factors and disciplines tangential to medical research, such as patient centered factors, costs and bias. This multifactorial complexity of medical decision making is depicted by The Medical Decision Making Model (modified) in Figure 2, defined by Chapman and Sonnenberg (2000). Specific focus of the discussion of this study's theory will be on the medical research pathway (MRP) components in the center vertical axis in the Medical Decision Making Model. This pathway conforms to the integrity of evidence-based practice. These are the steps in the MRP: 1. Clinical Research. 2. Probabilities. 3. Decision Models. 4. Guidelines. 5. Decisions. 6. Actions. While, all of the components shown in The Medical Decision Making Model are important factors in medical decision making, the MRP is most aligned with the goal of this study. The goal of this study is to provide survival probability insight for decision making purposes for AD patients who may need to be prescribed AAs for BPSD for evidence in the decision making process.

Figure 2

Medical Decision Making Model (modified)
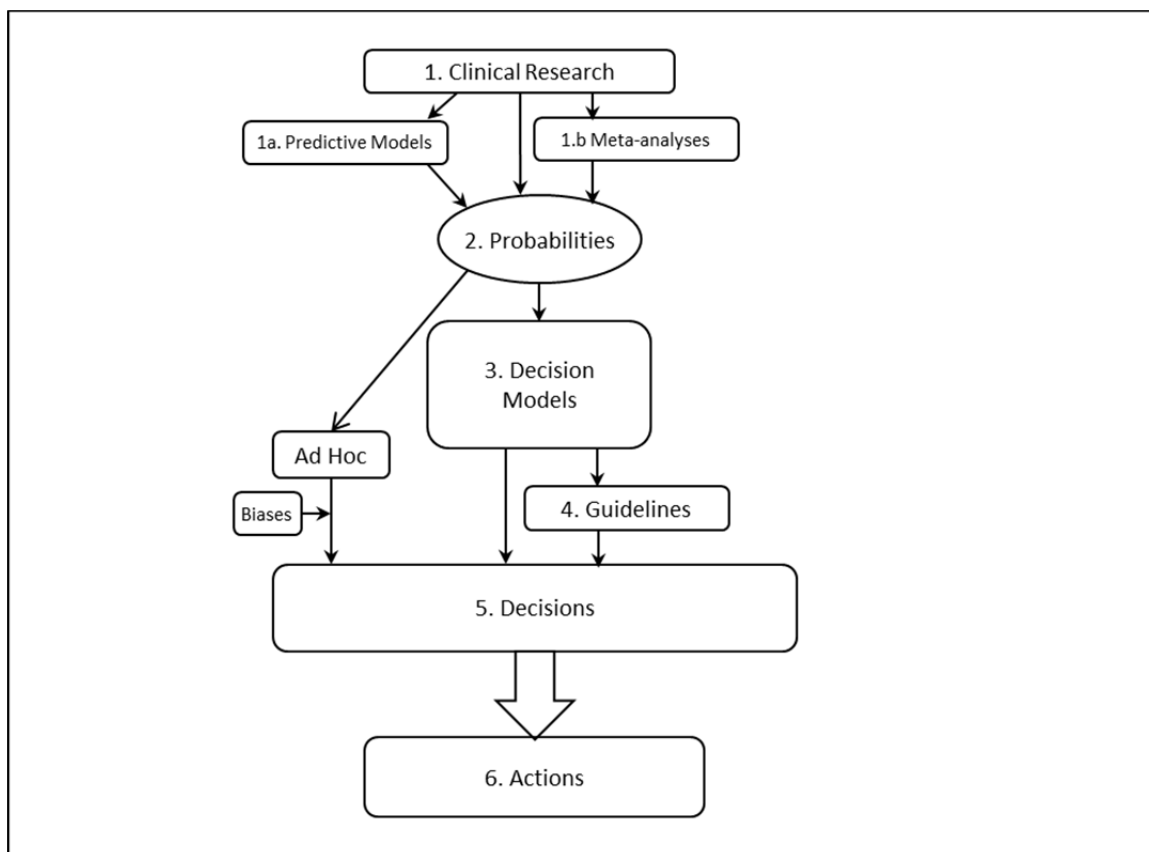
(G. B. Chapman & Sonnenberg, 2000)
Note: The full Medical Decision Making Model is in the Appendix

Medical research – the first step in the MRP

  The foundation of evidence-based practice is medical research, also identified as

Clinical Research in The Medical Decision Making Model (G. B. Chapman &

Sonnenberg, 2000). Medical research is experimental, or translational research, and its

purpose is to underlie medical knowledge (Zerhouni, 2003). While this study of AD

patients with BPSD taking AAs is technically not considered an experimental research

project, the gold standard of medical research, it meets the definition of a medical

research project. This is because it meets the criteria of a research effort that will

supplement medical knowledge. This study is technically an observational longitudinal retrospective analysis of administrative diagnosis data. However, the diagnosis data was derived from laboratory and diagnostic exams. The objective of the research is to extract survival probabilities from an administrative and medication prescription database of over 101 thousand patients over an 8 year period utilizing diagnosis and service date information on co-morbidities, age, gender, medication purchases and death dates. The dataset facilitates survival probability analysis based on co-morbidities.

Probabilities – the second step in the MRP

   Probability in medicine – defining uncertainty

Despite the wishes of patients, uncertainty is the norm rather than the exception in medical decision making (Gillett, 2004; Kemm, 2004; Scheidt, et al., 2004). Rather than certainty, most medical decisions are probabilistic (Lurie & Sox, 1999; Ratliff, et al., 1999). The crux of decision making in medical research is based on the utilization of probabilities to help refine choices in a clinical setting (M. Roberts & F. A. Sonnenberg, 2000). Probability is a quantitative estimate of event frequency (Pagano & Gauvreau, 2000). Ideally, probability can be most accurately estimated based on frequencies of historical observations of the same or similar events. In the case of medical event probabilities, comparing historical observations of equivalent medical events are the preferred method of generating probabilities. The results of the AD patients with BPSD and AAs study will focus on the probabilities of death events based on patient conditions (variables) in the sample of AD patients with BPSD taking AAs in the study. These probabilities can be used with and in decision models to help generate medical decisions, as discussed in more detail in the decision model section below.

Probabilities in the study of dementia and AA usage

Higher odds ratios in RCTs of dementia patients taking AAs over control groups of dementia patients not taking AAs spurred the Food and Drug Administration (FDA) in 2005 to investigate and later apply a black label warning on AAs for dementia patients. These probabilities have been reinforced by additional studies investigating the same circumstances outside of the 17 studies the FDA analyzed (Gill, et al., 2007; Helzner, et al., 2008; L. Schneider, et al., 2005). However, there have been no studies that have investigated circumstances and probabilities in greater depth or with more granularities. The objective of the dementia study with AAs is to expand the set of variables examined to include dementia subtype and diagnoses, with their estimated probabilities. This approach may give insight into conditions that could better answer why there is a higher death rate with dementia diagnoses taking AAs. This effort may also determine if there are dementia subtypes or diagnoses that show equal or better survival for the same patients.

Decision models – the third step in the MRP

Decision models provide a framework and methodology for weighting medical choices in order to compare them based on an expected value of outcomes. Outcomes can span a variety of dimensions, such as survival rates or life expectancy, quality of life and cost (M. Roberts & F. A. Sonnenberg, 2000). Decision models in a medical setting are critical in synthesizing the complexity of multiple probabilities for the multiple possible co-morbidities and conditions. Without decision models, complex medical cases can be nearly impossible to accurately assess, and therefore, are all-too-often left up to ad hoc decision making. The FDA arrived at the decision for the black label warning for

dementia patients and AAs by incorporating prior study probabilities into decision models that tested for life expectancy, as an example.

According to Roberts & Sonnenberg, 2000, decision modeling is a mathematical formula representation of a decision problem. There are many medical decision models available. All models need to incorporate four elements: perspective, context, appropriate complexity and a relevant timeframe. Perspective defines the values of the patient and the outcomes they wish, context defines the problem to be solved, appropriate complexity defines the scope and limitations of the model, and the time horizon needs to frame a realistic order and timeframe for the sequential desired outcomes (M. Roberts & F. A. Sonnenberg, 2000).

Decision trees

Decision trees are the standard, as well as most basic, of the many medical decision models that are available and utilized in the healthcare field. A discussion of the elements of the decision tree can provide a general understanding of what medical decision making attempts to accomplish, and how it can be accomplished with the most basic of elements. The following discussion will explain the basic decision tree model. The next discussion will use the example of this dementia and AAs study to illustrate how decision tree models work.

There are three major elements of decision models: 1. The model's structure., 2. The probabilities or likelihoods of the events in the model. 3. The utilities or values of the possible outcomes of the decision. In the case of the decision tree, as shown in Figure 3, the structure element is first made up of nodes and branches.

Figure 3

Basic Decision Model or Decision Tree
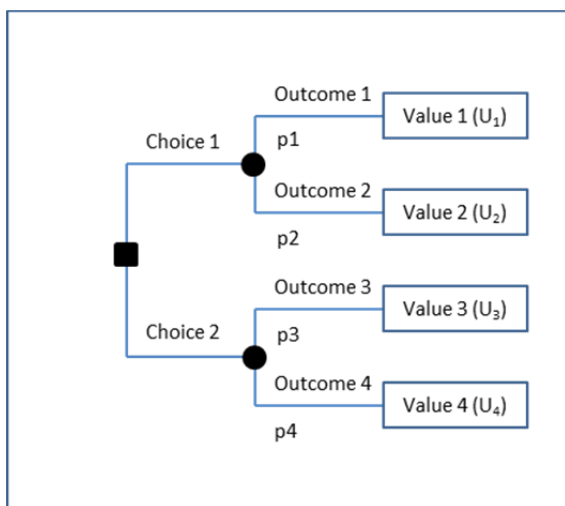
(M. S. Roberts & F. A. Sonnenberg, 2000)

Decision trees are a representative method of comparing medical decision alternatives and the expected outcomes of those alternatives (Sox, Blatt, Higgins, & Marton, 2007). The solid squares are decision nodes and represent two or more alternatives in a medical decision. The nodes, represented by circles, are the uncertain events that result from each alternative choice. The decisions can be any decision, such as decisions to operate or not operate, or to prescribe or not prescribe a medication, such as an AA, or even whether to provide or not provide palliative care. In Figure 3, decision branches are labeled choices (M. Roberts & F. A. Sonnenberg, 2000).

The second major element of decision trees is the chance nodes, which represent events or occurrences not fully under the control of the health care provider or decision maker. Because medical decisions carry uncertainty, these nodes are appropriately called chance nodes. Chance nodes are graphically represented as solid circles. These chance events generally result from the choices of each alternative, and each possible event is represented by branches labeled Outcomes in Figure 3. Outcomes can be various levels of

a cure, side effects, a specific change in medical status (or no change at all), or death or injury. In the case of tests or diagnostic decisions, the outcomes would be the test results, or possible side effects from the tests (M. Roberts & F. A. Sonnenberg, 2000).

Each branch of a chance node is represented by a probability which is the likelihood of occurrence of that event. Given each possible outcome has a level of uncertainty related to its taking place, each event or branch has an estimated probability assigned to it, represented by the small "p" in Figure 3. Probabilities of each set of branches from a chance node must add up to 1 or 100% (M. Roberts & F. A. Sonnenberg, 2000).

The third major element of the decision tree model is the utility or value of the possible outcome, represented by boxes in Figure 3 at the end of outcomes. In medical decision making, utilities have become a standard measure (Drummond, O'Brien, Stoddart, & Torrance, 1997). The concept of utility came out of economics and refers to preference. Preference can be measured in relative terms, such as decreasing or increasing, or along an ordinal scale, such as a Likert scale, or in other measures discussed below. When applied to medical decisions, utility is often a measure of a patient's expected preference or expected tolerance of a possible outcome from a medical action (Sox, et al., 2007).

Quality adjusted life years

A common utility or value system utilized in medical decision making is called quality adjusted life years (QALY). QALY consists of both life expectancy in years based on survival and a utility value representing the quality, or one's preference for a health state, in those years (Russell, 1999). The utility, if measured by time trade-off, is

the trade-off in years a patient in their current state of health would take compared to being either in perfect health for a certain number of years the patient versus being in ill health (Sox, et al., 2007).

   Decision tree method of analysis

   The standard method of analysis with decision trees is to arrive at an expected value for each alternative in the original decision node, what is referred to as expected values (G. B. Chapman & Sonnenberg, 2000; Sox, et al., 2007). The expected values represent the expected utility of going down each set of branches of each alternative. One expected value will be higher than the other possible expected values. Therefore, it is the desired decision choice because it maximizes your chances for receiving the most value. The standard for calculating expected values is referred to as "averaging out and folding back." Using Figure 4 as an example, the expected value for Choice 1 would be the probability of Outcome 1 multiplied by the utility value for Outcome 1 added to the probability for Outcome 2 multiplied by the utility value for Outcome 2. The expected value for Choice 2 would reflect the same formula using Outcomes 3 and 4.

   The mathematical formula using the symbols in Figure 4 would be

   Choice $1 = (p_1 * U_1) + (p_2 * U_2)$ Choice $2 = (p_3 * U_3) + (p_4 * U_4)$

Figure 4

Decision Tree with Average-Out and Roll Back

Outcome 1c
p_1
Value 1 (U_1)

Choice 1 = $p_1U_1 + p_2U_2$

Outcome 2
p_2
Value 2 (U_2)

Outcome 3
p_3
Value 3 (U_3)

Choice 2 = $p_4U_4 + p_3U_3$

Outcome 4
p_4
Value 4 (U_4)
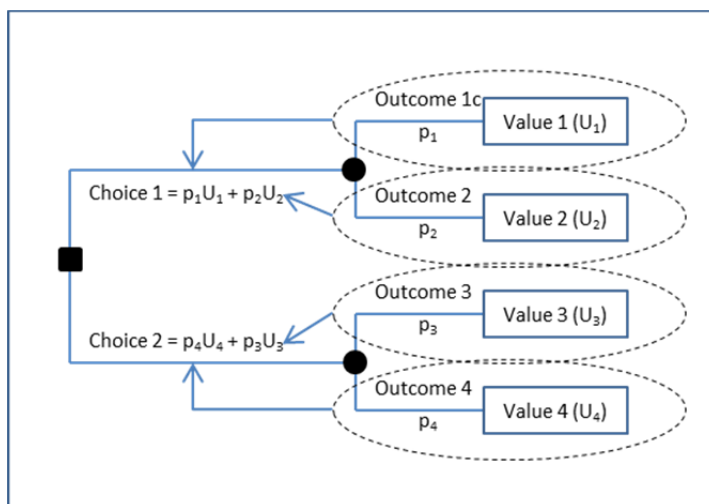
(M. S. Roberts & F. A. Sonnenberg, 2000)

More complex decision trees with branches that go beyond the simple decision tree in Figure 4 would expand the same simple additions of probability multiplied by value calculation for each chance node and outcome.

Other decision models

It should be noted there are a number of other medical decision models available. While the decision tree model has the highest prevalence of usage in clinical settings with patients, given it is the simplest and most straight-forward of the models, other models are often used in public health and guideline development. Two of the most prominently used decision models are Markov cohort simulations and Monte Carlo analysis (G. B. Chapman & Sonnenberg, 2000). These will not be discussed in detail within this paper, but suffice it to say both models are also based on probabilistic approaches.

Decisions – the fourth step in the MRP

Once decision models have processed patient condition information and probabilities, the results can form the basis of decisions, as represented in the fifth step in

the Medical Decision Making Model. The result of a decision model is to determine which alternative has the best chance of maximal value. But it is not the outcome that will actually happen to patients. In most cases there will still be an amount of uncertainty for patients (R. M. Kaplan & Frosch, 2005). The range of uncertainty can vary widely, in part based on the accuracy of the probabilities coming out of the decision models.

Decisions can range from a purely clinical nature, for example, whether or not to run more diagnostics, or which treatment or treatments are most appropriate. Each decision will possess unique probabilities. A decision tree can make these choices, uncertainties and utilities more visible and concrete. Patient input, as indicated in the Medical Decision Making Model, is an important factor in medical decisions. Involvement by patients in their own medical decisions with their physicians is often referred to as "shared decision making". Its use varies widely (Charles, Gafni, & Whelan, 1999). However, research has shown patient and family involvement in medical decision becomes even more important when treatment probabilities are relatively even, referred to as "equipoise" (Elwyn, Edwards, Kinnersley, & Grol, 2000). In these cases, the patient's decision making involvement may need to carry a much greater weight in the final treatment decision, also referred to as "preference sensitive" (Whitney, 2003). In these cases, decision trees may become a part of the patient's lexicon and understanding in order to make wiser decisions.

Medical action – the fifth step in the MRP

Medical action, as shown in the Medical Decision Making Model as "Action", is the bottom step in the flow of medical decision making along the MRP. Medical action is the carrying out of the decisions generated by all of the previous steps. Medical action

includes such things as executing surgery, prescribing medication, ordering physical therapy, ordering new diagnostics and a myriad of other medically oriented tasks. However, medical action is not the last process. As shown in the Evidence-based Practice Stepwise Pathway in Figure 1, the process is a circular one. After an action is executed based on evidence and patient preference, the results are then evaluated for further potential action. The ideal would be that no further action is needed and that the patient's condition that required action has been resolved.

Other components in medical decision theory relevant to the MRP

The following is a brief discussion of additional components of Medial Decision Theory that have bearing on the processes that are driving the AD with BPSD and AAs study.

Outcome assessments

The results of the treatments and/or diagnostics taken in the action step will generate new probabilities based on assessments of the outcomes of patients. These probabilities will flow back into individual cases for primary care providers to analyze for subsequent decision model processing and decisions. As an example, outcomes based on AA usage will continue to go back into the research on probabilities related to the conditions of AD patients with BPSD and its usage, for the individual patient case, as well as for broader research for a population of patients.

Databases

Hopefully, when the outcomes of many patients generate probabilities based on similar conditions and treatment, their combined data can become a part of healthcare databases, as depicted in Databases in the Medical Decision Making Model. These

healthcare databases can initially be clinical practice databases, research hospital databases, or government healthcare agency databases, samples of which flow into large medical research studies.

Guidelines

It is the objective of this study to provide additional data points (probabilities) for future decisions through informing guidelines related to AD patients with BPSD potentially needing AAs as a treatment option. When clinical research, utilizing data derived from outcome databases, repeatedly shows efficacy or significant results in many studies, as depicted by Meta-analyses in the Medical Decision Model, guidelines by professional associations, government healthcare regulatory agencies or healthcare delivery organizations are often developed to help in expediting and standardizing decisions. The Guidelines step is shown in the Medical Decision Model. Guidelines become a very important part of evidence-based practice over time and have been shown to significantly improve healthcare (McGlynn et al., 2003).

Methodology

Research Design

This is a retrospective observational survival analysis of AD patients with BPSD taking AAs with case controls of AD patients with BPSD not taking AAs using administrative records over an 8-year period (January 2001 to December 2008). Duration from first diagnosis of BPSD to death is the primary measure period. Durations are tracked for each subject for up to 3 years. The start of these 3-year tracking periods can start at any point between January 2001 and December 2005. Propensity score matching methodology was used to pair match treatment and control cases by acuity level in order to resolve confounding and bias issues inherent in observational studies. Kaplan-Meier Method and Cox Proportional Hazards Model were used to establish whether there were statistically significant differences in mortality rates between groups (Breslow, 1975; E. L. Kaplan & Meier, 1958) . These survival analysis methodologies are the most widely used statistical methods for longitudinal mortality studies when comparing distinct group death outcomes (Singer & Willett, 2003).

Description of Research

Setting

The patients included in this study are members of Kaiser Permanente (KP), an integrated managed care organization (MCO) consortium that operates in a number of states and the District of Columbia. Kaiser Permanente Northern California (KPNC) is the largest region in the five region KP system, with 3.2 million members. There are 21 medical centers in KPNC. KP medical centers provide healthcare in company-owned and managed outpatient clinics and hospitals, as well as through an integrated full-service

inpatient and outpatient pharmacy. Most skilled nursing facilities are contracted to private organizations.

Variables

The two primary variables, time to death as the dependent variable, and AA usage as the independent variable, will answer the following research question: do AD patients with BPSD using AAs die earlier than those AD patients with BPSD who are not using AAs?

Atypical antipsychotic usage

AA usage is the independent variable. The AA medications in this study include (trade name in parentheses): quetiapine (Seroquel), olanzapine (Zyprexa), and risperidone (Risperdal). All of these AAs are part of the formulary of KPNC and the only AAs dispensed to the patients in the study.

Defined use of AAs is not based on an observed ingestion or a recording of the taking of the medication. Rather, the proxy for the ingestion is the recorded dispensing of the medication to the patient. It is not known how well the patients complied with the taking of the medications. We assumed in this study that patients were fully compliant during the period of each unique dispensing.

Covariates for dosage strength, frequency of use, and flexibility in dosing and frequency are also incorporated into the study. Many of the prescriptions could be taken as needed, and/or allow subjects to increase or decrease the dose based on the severity of their symptoms. In order to create variables for dosing frequency and flexibility in this study, a computer program parsed prescription instructions for every prescription to break out these variables.

Medication compliance over multiple dispensed prescriptions is included in the study. The compliance methodology used in the study is the medication possession ratio (MPR), which has been a standard compliance measurement formula in pharmacology studies (Al-Zakwani et al., 2003), in particular for retrospective studies (Peterson et al., 2007). Medication compliance studies of AAs utilizing the MPR metric has shown an association between emergency room utilizations and higher adherence (Al-Zakwani, et al., 2003). The calculation for MPR is simple: the number of pills/days the patient was prescribed is divided by the cumulative period of time the patient was prescribed the medication. Gaps in prescriptions will render the MPR less than 1 and no gaps will result in an MPR of 1.

Time to death

The dependent variable, time to death, or duration until expiration, is operationalized in months, from first diagnosis of BPSD, after a first dementia or AD diagnosis, to date of expiration, for both AA users and non-users. Duration is the key measure in survival analysis and is independent of dates. Duration is the primary comparison for the following research question – is the duration from first BPSD diagnosis to death shorter for AD patients with BPSD who have been prescribed AAs when compared to those who have not been prescribed AAs?

Death from BPSD diagnoses start, rather than AA start, is based on an objective of this study to analyze AA use within the timeframe of BPSD and not exclusively the time frame of AA use. One of the advantages of this approach is that it gives a concrete start date for both the treatment case and the control (non-treatment) case in a matched pair case controlled survival analysis. In some of the observational studies previously

referenced, start dates for non-AA use are estimated (Gill, et al., 2007). Case controls are

matched with the treatment case based on acuity levels. The assumption is that the same

acuity levels possess equal survival rates. The assumption of this study is that the need

for AA treatment is based on BPSD, and therefore the diagnosis of BPSD is a valid start

date.

   Measures and statistical analysis

      Survival analysis

      The statistical method to calculate differences in time to death between the use

and non-user groups will be done using survival analysis. Survival analysis is an area of

statistics that specializes in comparing time until one or more events occur. It is used

widely in life sciences in measuring time to death. The statistical problem addressed

using survival analysis is often characterized as competing risks analysis. Risk

comparison is the statistical outcome assessment of this study, i.e., risk of death between

AA use and AA non-use. Risk assessment can be put either in terms of survival risks, i.e.,

probability of surviving, or hazard risk, i.e., probability of dying. Hazard risk is

sometimes referred to a failure risk (Kleinbaum & Klein, 2005). Survival analysis in this

study is presented using two methodologies, Kaplan-Meier survival estimations and Cox

proportional hazards.

      A key characteristic of survival analysis is in statistically factoring those cases

where the event of interest is either never observed and experienced, or observed and

experienced outside of the study timeframe. In most survival studies, it is rare that 100

percent of the subjects will experience the event of interest during the study (Pagano &

Gauvreau, 2000). In order to account for subjects who do not experience the event of

interest over the time frame of a study, survival analysis marks those subjects as censored and removes them from statistical analysis after the censor event. Prior to the censor event they are a part of the statistical analysis. This statistical process of accounting for censoring of subjects is one of the distinguishing elements of survival analysis (Hosmer, Lemeshow, & May, 2008). Censoring can occur at any point in the study except time zero. There are two types of censored patients in this study. The first type includes those who have BPSD diagnosis to death durations greater than 3 years. The second type is those who are lost to follow-up where there is no record of whether they are alive or dead after 3 years from their first BPSD diagnosis. Based on standard procedures for survival analysis, the first type is censored at 36 months and the second type is censored at their last utilization (Breslow, 1975; E. L. Kaplan & Meier, 1958; Singer & Willett, 2003).

Kaplan-Meier survival estimations

Kaplan-Meier method estimations for continuous-time survivor function probabilities provide a non-parametric binomial analysis of survival (E. L. Kaplan & Meier, 1958). Its strength is in univariate analysis (Allison, 2010). For this study, it is utilized in assessing the primary outcome or dependent variable of death against the primary independent variable of AA use. Kaplan-Meier survival estimation curves provide a visual presentation of the analysis. Kaplan-Meier does not provide predictive coefficient estimates. Therefore, it does not provide a method to measure the effect of covariates on survival time (Singer & Willett, 2003). Its primary value is in establishing the baseline analysis: is there a statistically significant relationship between the independent and dependent variables? In this study, it is the relationship between AA use and death.

Within the Kaplan-Meier survival analysis in this study, hypothesis testing is judged primarily by log-rank results. The log-rank test is a form of a chi-square test. It is particularly suited for large sample analysis and is the most widely used of the hypothesis tests for survival rates (Allison, 2010).

One of the advantages of the Kaplan-Meier survival analysis method is that its results can be represented graphically. Survival probability is represented along the y-axis, starting at 1.0 at time zero and declining, and time is represented along the x-axis, starting at time zero. Censored cases are represented by plus signs (+) and marked at the time point of the censoring.

Cox proportional hazards

The second methodology, Cox proportional hazards (Breslow, 1975), utilizes semi-parametric log regression algorithms to analyze both univariate (unadjusted) and multivariate (adjusted) risk probabilities of the hazard of death. Probabilities derived from hazards analysis are different probability estimations from Kaplan-Meier survival estimations. Survival estimations generate a probability of surviving at any single point along a duration continuum, whereas hazards analysis generates a probability of dying at any single point along a duration continuum. Cox proportional hazards algorithms are distinguished from Kaplan-Meier estimations in their ability to factor covariates and predict outcomes between two groups utilizing hazard ratios (Kleinbaum & Klein, 2005). Hazard ratios are a form of odds ratios and can be treated as odds ratios when calculating probabilities (Allison, 2010). The conversion of hazard ratio (HR) to probability: probability = HR / 1 + HR.

Cox proportional hazard results are shown in two forms: first, unadjusted, other than AA usage, and second, adjusted (with covariates). The objective of the unadjusted results is to test if the variable for use of AAs has an independent effect without controlling for any other covariates. The objective of the adjusted analysis is to show how well the results hold up against the effect of multiple covariates. Analyses of covariates will be shown when they have a statistically significant impact on the results.

Sample

    Criteria for sample selection

       The study inclusion criteria are the following: 1. Living patients at entry. 2. Aged 65 or older at entry. 3. Diagnosis of AD., 4. A diagnosis of BPSD on or after their first diagnosis of AD. 5. At least one KP resource utilization between the years 2001 and 2008 in KP Northern California with a simultaneous diagnosis of AD and BPSD. 6. The AA use group, containing at least one prescription for one of the three AAs in the KP formulary, risperidone, quetiapine, and olanzapine.

       The following are rationale behind the decisions related to study criteria inclusion noted above. First, living patients at entry were chosen because this is a study about mortality rates, and therefore the subjects must be living at entry into the sample in order to measure the time until death. Second, only subjects aged 65 or older at entry were included in order to ensure comparability to comparative studies. Most studies investigate dementia as a disease of the elderly, which by and large is considered to be age 65 and older. This study excluded early onset dementia, dementia in ages less than 65. Third, a predominant diagnosis of AD, where utilization diagnoses of AD are greater than 50% of the total utilization diagnoses of dementia and/or an AD diagnosis at death. Those subjects with mixed dementia, which include those with a diagnosis of AD and vascular dementia, were not included in this group. Fourth, a diagnosis of BPSD on or after the dementia diagnosis, excludes those patients who received a diagnosis of BPSD or BPS before a diagnosis of dementia. As shown in Table 1, identified as "Non-post dementia diagnosis BPSD", there were 2,427 cases of AD patients who received a BPSD or BPS diagnosis prior to their first dementia diagnosis. Fifth, active KP resource utilizations

between 2001 and 2008 were required to ensure accurate information about covariates, death and medication use was available for each subject. Finally, sixth, for the AA treatment group, at least one prescription of one of the KP formulary AAs on or after a BPSD or BPS diagnosis was required to establish the inclusion into the treatment group. Those cases where the first AA prescription occurred before a BPSD or BPS diagnosis were excluded from the final study sample. This was in order to ensure medication treatment was related to AD and BPSD incidence, and not AD alone or BPSD alone or other factors unrelated to AD or BPSD.

Data collection methods

This study is an observational retrospective using secondary electronic administrative databases. Informed consent for inclusion in studies is obtained from KP members at the time of their joining KP as a member. The health service data for this study was collected electronically from KPNC Management Information and Analysis (MIA) databases for clinic, inpatient, skilled nursing facility, home health and hospice. AA dispensation data was collected electronically from the KPNC Pharmacy Information Management System (PIMS) database. Use of antipsychotics is recorded based on the incidences of dispensing to the patient in the database. Death records were also collected electronically from the KPNC Patient Demographic database, which tracks death from all sources by social security number. Other sources of death records outside of KP in the KPNC Patient Demographic database include Social Security databases and local government death certificate databases.

Dementia cohort database

The original cohort from whom the final study sample of 3,140 patients was derived was composed of 101,156 dementia patients. This cohort database tracked the clinical history of every patient visit to clinic, inpatient, skilled nursing facility, home health, hospice, surgery, dementia related pharmacy and emergency rooms over an 8 year period, from January 1, 2001 to December 31, 2008. It also tracked hospitalizations and skilled nursing facility utilizations from January 1, 1994 to December 31, 2000, as well as outpatient utilizations from January 1, 2000 to December 31, 2000. The main objective of the database was to analyze prevalence, incidence and frequency of disease conditions and utilizations based on diagnoses and resource visits. It is this cohort clinical database that serves as the population data for this study. AD and BPSD diagnoses were based on International Classification of Diagnosis version 9 codes (ICD9). A list of ICD9 codes utilized for this study can be found in the Appendix

The pre-case matched samples were derived from a final database of 82,160 dementia patients during the years 2001 to 2008. This is a reduction from the original cohort database of 101,157 dementia patients, as shown in Table 1. The first subjects excluded were those with first diagnoses as early as 1994 when the dataset only included utilization records from inpatient and skilled nursing facility settings. Excluding those who had died prior to January 1, 2001 or who did not have utilizations after December 31, 2000, reduced the database to 82,160 patients. A data cleaning process eliminated 2,050 patients with birth dates, first diagnoses, medication and death dates which were not possibly correct. An additional 4,700 patients were deleted from the final sample who were patients in the original cohort database with a diagnoses of mild cognitive

impairment or "Other persistent mental disorders due to conditions classified elsewhere including cognitive disorders non-specific" (ICD9 294.9), as well as unspecified gender. Another 2,388 patients were deleted who were less than 65 years old with early onset dementia.

The final series of exclusions were related to AD and BPSD criteria, as shown in Table 1. There were 51,581 patients who were not designated as AD diagnosed patients and these cases were excluded. Case dementia subtype diagnoses are mutually exclusive. Of the inclusive AD cases, there were 15,168 cases who had never received a BPSD or BPS diagnosis and these were excluded. Finally, there were 2,427 cases of AD patients with BPS diagnoses who received a BPS diagnoses prior to a first diagnosis of dementia. These were also excluded.

Table 1

Dementia Cohort Database to Final Sample Reduction

Description	Subjects	Remainder
Original cohort database	101,157	
Pre-2001 patients dead or no utilization	-18,997	82,160
Corrupted data	-2,050	80,110
Unspecified cognitive disorders & gender	-4,700	75,410
Dementia diagnosed patients under 65	-2,388	73,022
Non-AD cases	-51,581	21,441
Non-BPSD AD cases	-15,168	6,273
Non-post dementia diagnosis BPSD	-2,427	3,846
Final cohort population database	3,846	

AD with BPSD sample characteristics

Of the final AD with BPSD cohort database of 3,846, 2,167 subjects were AA users and 1,679 subjects were non-AA users, as shown in Table 2. A final exclusion of those AA patients who had received their prescription of AAs prior to a diagnosis of BPSD eliminated an additional 595 cases, leaving 1,572 AA users and 1,667 non-users

with diagnoses of AD and BPSD. It was this sample which was used to create the final

case matched sample for survival analysis.

Table 2

AD with BPSD Sample Prior to Case Control Matching – AA Use and Expirations

Description	AA users		Non-AA users		Total Subjects
Final cohort population database	2,167	100%	1,679	100%	3,846
AA prescription prior to BPSD dx	-595	-27%	n/a	0%	-595
Pre-case control selection sample	1,572	73%	1,679	100%	3,251

Propensity score matching case control selection

The objective of case control selection is to reduce bias and confounding in

observational studies by matching treatment cases with control cases based on equivalent

acuity levels (Guo & Fraser, 2010). One of the weaknesses of observational studies

designed to compare differences between treatment and control groups is the potential for

confounding and unexplained variance between treatment and control groups due to

unequal acuity. Experimental random control trials attempt to reduce confounding and

bias by tightly controlling study inclusion criteria based on acuity combined with random

assignment to treatment and control groups (Austin, Grootendorst, & Anderson, 2007). In

an observational study, a control group unexposed to the treatment may have very

different acuity levels than the treatment group, which could lead to significant bias in

predicted outcomes between the two groups, even if traditional covariance analyses are

utilized to control for unequal acuity (D'Agostino, 1998).

Case control matching in this study is accomplished by the propensity score

matching (PSM) technique. The objective of the PSM process in this study is to match

expired AA non-users with expired users utilizing a set of variables that predict

"propensity" to take AAs for users and non-users based on their acuity. PSM attempts to balance the selection of case and control groups by statistically modeling an acuity score, which can then be used to match groups and/or pairs of cases within case and control samples such that they would have equal probability to have been candidates for treatment (Rosenbaum & Rubin, 1985).

PSM involves three steps. The first step is covariate selection. This was accomplished by executing a logistic regression analyses to find statistically significant covariates that reflect patient acuity. This step has been defined in PSM medical studies and specific dementia with AA observational studies using PSM techniques (Charlson, Pompei, Ales, & MacKenzie, 1987; D'Agostino, 1998; Deyo, Cherkin, & Ciol, 1992; Gill, et al., 2007). The covariate variables include age and sex, along with the variables in the following groups: Charlson Comorbidity Index, cognitive diagnoses, psychological diagnoses, memory medications and resource utilizations with a focus on inpatient, neurology and psychiatric visits. Specific variables are defined below in the case control variable section. Covariate inclusion and exclusion was based on a backward selection of the covariates using the LOGISTIC procedure in SAS 9.2 (PROC LOGISTIC). This process assigned an acuity probability for each case in the full sample.

The second step involves the establishment of the PSM parameters: these are based on the probability score derived in step one. Treatment and controls are matched based on a caliper of the proximity of their probability score to each other. The caliper for this study is based on the probability and specific standard deviation of the probability scores in the sample. Based on a number of calipers utilized in other PSM studies (Austin, Grootendorst, & Anderson, 2007; Brookhart et al., 2006; Gill, et al., 2007), in

addition to a number of experiments with different standard deviation calipers within in this study, the standard deviation settled on was 0.10 of the sample's probability set standard deviation.

The third step in the process involves matching, which pairs treatment and control cases. Based on papers which analyzed various PSM techniques (Austin, et al., 2007; Brookhart, et al., 2006), a "greedy" matching, also referred to as matching with replacement, process was selected as the most appropriate. Matching with replacement is matched to the nearest control patient, even if a control is matched more than once. Matching without replacement is used when there are few controls similar to the cases (Guo & Fraser, 2010).

The matching process was executed by a SAS 9.2 program, with modifications, published in a conference paper, *"Local and Global Optimal Propensity Score Matching"* (Coca-Perraillon, 2007), referenced by a number of studies. The program included a number of options, of which the caliper and matching with replacement options were selected as appropriate for this study. Usually the selection of the matching method depends on the degree of overlap between the propensity scores of the cases and the controls.

The final number of cases, 3,140 patients, in the study was reduced at this step because not all treatment cases could be matched with a control case. In order to be included in the final analysis, treatment and controls would have to qualify for matching based on their fitting within the caliper requirement of their probability for AA use. Cases which did not have a qualifying caliper match would be eliminated from the final analysis. As shown in Table 3, 1,570 treatment cases qualified and 2 treatment cases did

not qualify for final matching with a control case. The final control case total must match

the treatment case total because matching is pair based, each treatment case must

therefore be matched with a control case. Consequently, the case control total is also

1,570 subjects.

Table 3

Final AD with BPSD Sample – Before and After Case Control Matching

Description	AA users		Non-AA users		Total Subjects
Pre-case control selection sample	1,572	100%	1,679	100%	3,251
Post case control selection sample	1,570	99.9%	1,570	94%	3,140

Case variables

Below are the groups of case covariates and the reasons for their inclusion in the

study.

Charlson Comorbidity Index

The Charlson Comorbidity Index is a standard methodology for classifying

comorbid conditions to assess risk in clinical studies (Charlson, et al., 1987). The

conditions that comprise the Charlson Comorbidity are used for propensity score

matching for case control assignment and comorbidity analysis in this study. The criteria

for these conditions are based on the ICD9 diagnosis codes (Deyo, et al., 1992). The

Charlson Morbidity Index was not originally designed and tested based on ICD9 codes.

However, Deyo et al. (1992) ICD9 designations have become widely used in conjunction

with the Charlson Morbidity Index (Schneeweiss & Maclure, 2000). The following are

the medical conditions of the Charlson Comorbidity Index: myocardial infarction,

congestive heart failure (CHF), peripheral vascular disease, cerebrovascular disease,

chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver

disease, diabetes, diabetes with chronic complications, dementia, hemiplegia or paraplegia, renal disease, any malignancy, including leukemia and lymphoma, metastatic solid tumor and AIDS.

Heart and vascular variables

Variables for hypertension and cerebral vascular accidents (CVA), in addition to the Charlson Comorbidity Index condition CHF, are included as covariates in the study, based on a number of studies that have shown an associative relationship with dementia and cardiovascular disease (ADAPT, 2006). Based on a theory that pacemakers and implanted heart defibrillators may be protective of mortality risk in this population (Park-Wyllie, et al., 2009), covariates for the presence of pacemakers and implanted heart defibrillators are also included in the study.

Cognition and psychological variables

The cognition and psychological variables included were depression and altered mental status. In some studies, depression has been associated with dementia acuity (Ohanna, Golander, & Barak). While altered mental status differs from dementia because of its short term nature, some studies have shown a relationship with dementia acuity during hospitalizations (Fick, Agostini, & Inouye, 2002).

Memory medications

Memory problems are a hallmark of dementia and the use of anticholinesterases and other memory medications are used extensively by AD patients with BPSD (Bird, 2010). The use of memory improvement medications donepezil (Aricept) and memantine (Namenda) have been included as possible covariates in this study. Aricept and Namenda

are the only memory improvement medications in the KP formulary and therefore the only memory improvement medications prescribed for subjects in this study.

Resource utilization variables

Utilizations of various healthcare resources, in particular inpatient utilizations, have been shown to be associated with acuity levels of dementia patients (Al-Zakwani, et al., 2003; Hill et al., 2002; Quinlivan et al., 1995; Zubenko, Rosen, Sweet, Mulsant, & Rifai, 1992). Therefore, this study included variables for the inpatient, emergency room, clinic, skilled nursing facility, home health and hospice visits. The clinic visit variables were limited to those related to dementia care as specialties: neurology and psychiatry. Neurology and psychiatry are where the majority of diagnoses occur for AD patients with BPSD outside of their own primary care providers within the KP outpatient clinic setting.

Additional geriatric high acuity variables

Three additional variables that previous studies have found were indicative of dementia patient's acuity levels, but which are not found in the Charlson Comorbidity Index were included in the covariate list (Fahey, Montgomery, Barnes, & Protheroe, 2003; Gurwitz et al., 2005). These are related to high acuity geriatric cases and include fecal incontinence, urinary incontinence and a history of falls.

Case variable incidence

An incidence analysis of the study case variables, or covariates, by the two groups of AA users and non-users in the final sample, as shown in Table 4, indicates good balance was achieved with the propensity score matching, with only a few exceptions. All covariates were dichotomous with the exception of one covariate, age, which was continuous. All covariates between the AA groups reflect a less than a 4% difference and

most all were found to have statistically insignificant differences between the groups using Pearson chi-square analysis for the binary covariates and t-test analysis for the one continuous covariate, age. Therefore, good acuity equivalency was achieved between the treatment and control groups, thus helping to decrease the effect of confounders and bias.

There were three exceptions to the less than 4% difference between covariates: history of myocardial infarction (Chi-square (df) = 7.269 (1), p = 0.007), peptic ulcer disease (Chi-square (df) = 4.7983 (1), p = 0.0285) and diabetes with chronic condition, (Chi-square (df) = 5.0246 (1), p = 0.025). All three variables were tested for significant differences over time using general linear mixed model analysis, as prescribed by Hosmer, et al. (2008), and were found not to have a significant impact on predictor covariate selection in the final Cox proportional hazard models.

Table 4

Covariate Distribution – AA Users versus Non-Users

Variable Description	AA users		Non-AA users	
	N	% of group	N	% of group
Demographics				
Age (years old at first BPSD diagnosis)	82.2		82.5	
Male	568	41%	546	39%
Female	816	59%	838	57%
Medical History (over period of diagnosis)				
Myocardial infarction	291	21%	328	24%
Congestive heart failure	323	23%	367	27%
Peripheral vascular disease	146	11%	172	12%
Cerebral vascular accident	370	27%	392	28%
Chronic obstructive pulmonary disease	414	30%	419	30%
Rheumatologic disease	36	2.6%	34	2.5%
Peptic ulcer disease	74	5%	88	6%
Mild liver disease	7	0.5%	9	0.7%
Severe liver disease	3	0.2%	9	0.7%
Diabetes	299	22%	271	20%
Diabetes with chronic conditions	164	12%	136	10%

Variable Description	AA users		Non-AA users	
	N	% of group	N	% of group
Paraplegia	32	2%	21	2%
Acute renal failure	399	29%	382	28%
Cancer diagnosis	237	17%	256	18%
Metastasized cancer	50	4%	53	4%
Hypertension	1,047	76%	1,093	79%
Pacemaker	69	5%	77	6%
Depression	659	48%	633	46%
Dementia Severity (over period of diagnosis)				
Urinary incontinence	340	25%	328	24%
Fecal incontinence	50	4%	54	4%
History of falls	96	7%	67	5%
Screen for dementia	389	28%	389	28%
Psychosis post dementia dx	40	20%	37	18%
Cognitive Problems				
Altered mental status	290	3%	294	3%
Mild cognitive impairment pre-dementia	64	1%	94	1%
Medications (over period of diagnosis)				
Aricept prescription	775	56%	784	57%
Namenda prescription	314	23%	274	20%
Healthcare Contacts (average over period of diagnosis)				
Emergency room	10.7		10.7	
General medicine	30.9		29.5	
Home health	2.2		2.2	
Inpatient	9.2		8.6	
Neurology	4.1		4.1	
Psychiatry	5.0		4.6	
Skilled Nursing Facility (SNF)	2.4		2.0	

Results

Descriptive Statistics

Distribution of durations

The time period or duration from first BPSD diagnosis to death is the critical measurement of the study. The frequency distribution of this measurement over the 36 months of the study is shown in Figure 5. In survival analysis studies, the standard measurement of central tendency is the median (Hosmer, et al., 2008; Singer & Willett, 2003). There is a wide difference in the median months of time until death after first BPSD diagnosis. The median of the duration until death of AA users is 18.1 months, while the median of non-AA users is 6.3 months, nearly a one year difference at 11.8 months. The median of all subjects is 11.9 months. Out of the total sample of 3,140 subjects, 1,575 subjects died during the study and 293 subjects died after the study, uncensored and censored respectively, for a total 1,868 subjects who died. There were 1,272 subjects who did not die during or after the study ended, representing 41% of the study. Detail on the censoring distribution of the above is given in the Appendix in the *Censoring Distribution* section.

Figure 5

Duration Distribution of Atypical Antipsychotic Users versus Non-users
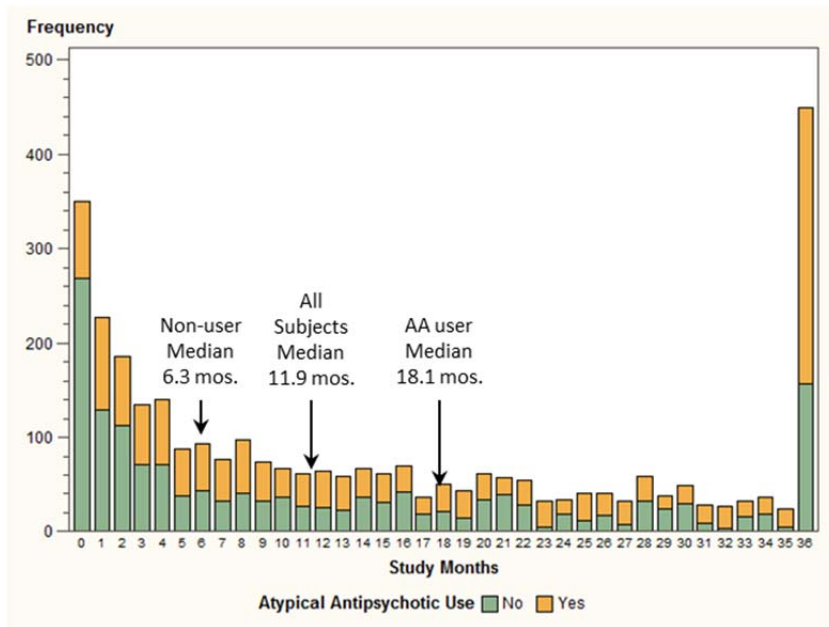
The cumulative death rate analysis between AA users versus non-users further reinforces the earlier death rate for non-users, as shown in Figure 6.

Figure 6

Cumulative Death Rate for Atypical Antipsychotic Users versus Non-users
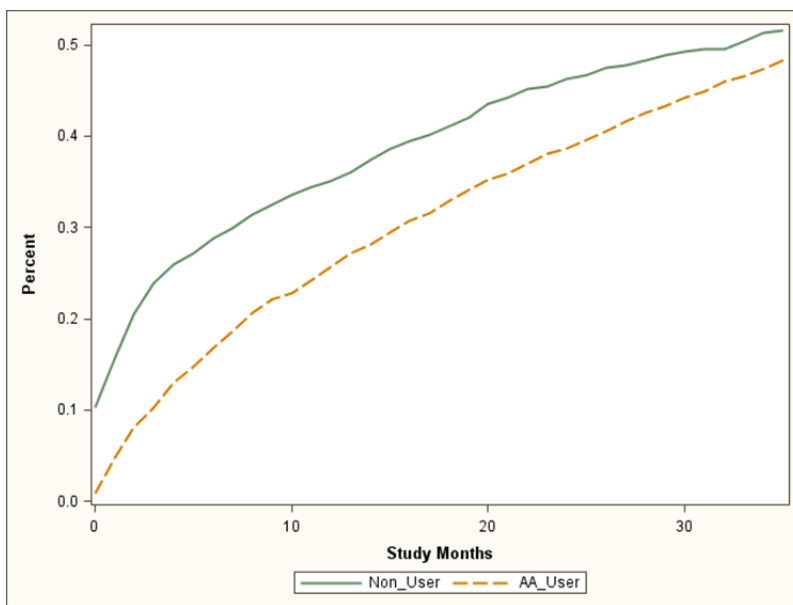
Medications

The study included three AA medications, reflecting the KP formulary (trade name in parentheses): quetiapine (Seroquel), olanzapine (Zyprexa), and risperidone (Risperdal). Quetiapine was taken by over half the user group, 51.1%, followed by Risperidone, 50.6% and olanzapine, 35.4%. This medication use indicates AA subjects used multiple medications over the study period: 69% of users were prescribed only one AA medication, 25% were prescribed two medications and 6% were prescribed all three medications.

Table 5 delineates AA usage in single and multiple medication situations by medication. Quetiapine is the leading AA prescribed for AD with BPSD patients, followed by risperidone and olanzapine. In the two medication cases, risperidone and quetiapine are the most frequently prescribed at 11%, followed by risperidone with olanzapine, and olanzapine with quetiapine, both at 7%.

Table 5

AA Combinations of Single versus Multiple AA Medications

Medication Combinations	N	%
Quetiapine	424	27%
Risperidone	415	26%
Olanzapine	236	15%
Single AA Subtotal	1,075	68%
Risperidone & quetiapine	175	11%
Risperidone & olanzapine	117	7%
Olanzapine & quetiapine	116	7%
Double AA Subtotal	408	26%
All AAs	87	6%
Total	1,570	100%

Medication duration

The median prescription duration of AA usage is 11.2 months as shown in Figure 7. This is close to the median duration of BPSD for all subjects, which is 11.9 months.

Figure 7

Distribution of Total Time on AAs in Months
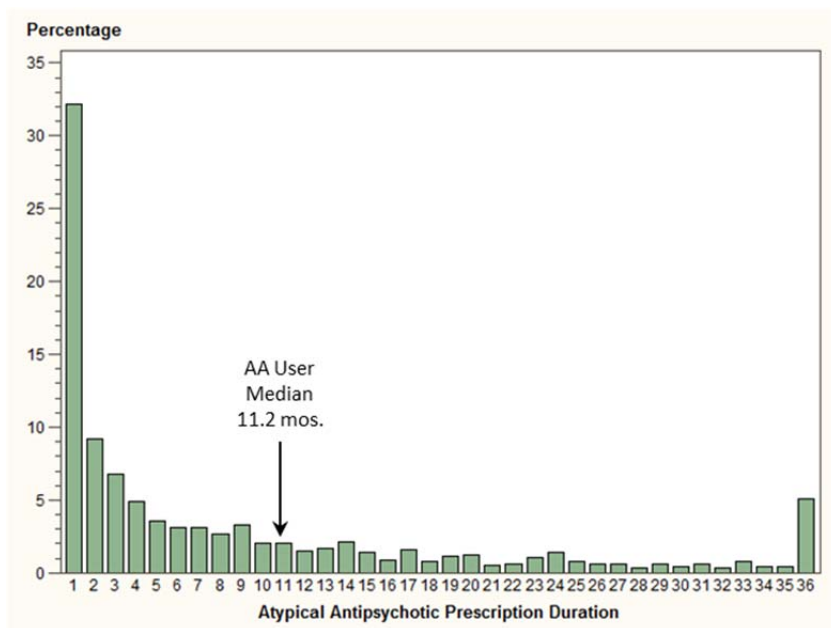
Compliance

Not all medications are prescribed to be taken continuously and not all patients take their medications continuously, even if they are instructed to take their medications continuously. The medication possession ratio (MPR) has become one of the standard metrics for measuring continuous use and compliance (Al-Zakwani, et al., 2003), as discussed in the Methodology section. The distribution of MPR scores for this study indicates 56% of all AA cases matched prescription and dispensing instructions, represented by the MPR score of 1.00., as shown in Table 6. The scores under 1.00 represent cases where the prescription period was longer than the number of doses they should have taken over the entire period of their AA prescription. This means that there

were gaps where they were not taking the medication at all or took fewer pills than

prescribed.

Table 6

Distribution of MPR Scores

MPR Score	N	%	Cumulative %
0.1	11	1%	1%
0.2	42	3%	3%
0.3	42	3%	6%
0.4	91	6%	12%
0.5	111	7%	19%
0.6	113	7%	26%
0.7	101	6%	33%
0.8	87	6%	38%
0.9	86	5%	44%
1.00	886	56%	100%
	1,570	100%	

There is a group within the 1.00 group, "RX1", which reflects patients who

received only one AA prescription. Technically, this group should be a MPR of 1.00, but

for analytical purposes of this study, this group was given its own subgroup. This is an

important group to analyze separately. The 1.00 subgroup represents 13% of the entire

MPR grouping mix, as represented in Figure 8. The one-time prescriptions cases died

very close to the start of their prescription period, with 98% of the patients dying within 3

months of the start of their prescription, as shown in Table 7.

Figure 8

Distribution of Medication Possession Ratio by Decile Grouping
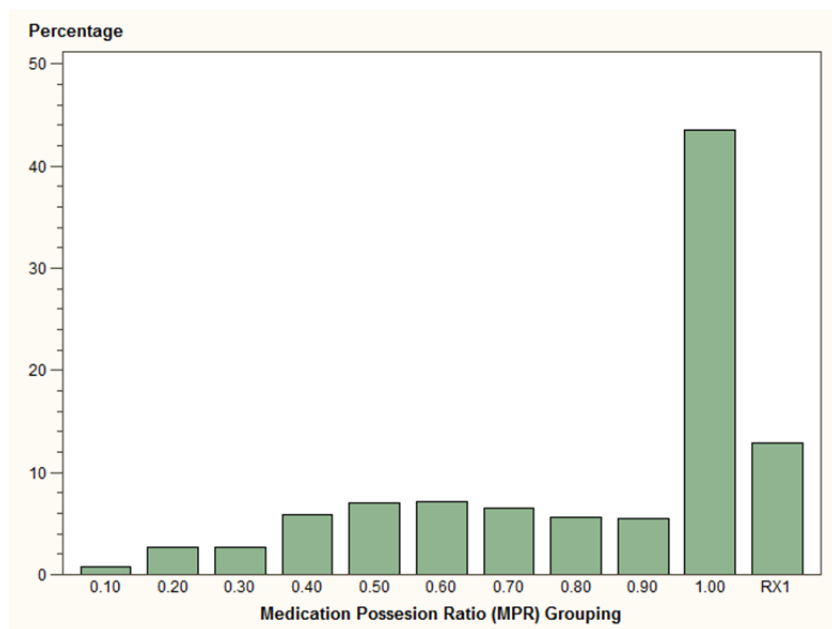
Table 7

One-time Prescriptions – Death After Prescription Start

Month from prescription start	Deaths	%
Month 1	262	62%
Month 2	88	21%
Month 3	65	15%
Months 4-7	8	2%
	423	100%

Dose strength

The prescribed doses for the AA uses in the study ranged from less than 1 of the standard minimum dose for the medication, as defined in psychotropic medication manuals (Keltner & Folks, 2005; Lehne, 2004), to as much as 10 times the minimum dose. The distribution of dosing possessed natural breaks. As shown in Table 8, 61% of the patients received dose strength 3 times or more the minimum dose.

Table 8

Dose Strength as Prescribed

Dosing Strength	AA Patients	
	N	%
Less than or equal to 1	394	25%
Greater than 1 to 3 times	561	36%
Greater than 3 to 5 times	300	19%
Greater than 5 times	315	20%
Total	1,570	100%

Dose frequency and changes

While the dosing instructions of the AA prescriptions indicated some flexibility in 15% of the cases, 85%, required the patient to take the AA medications daily. Additionally, there was no flexibility to be able to increase the dose on an as needed basis, with no dose increase indicated in 97% of the cases, and only 3% of the cases were allowed to increase the dose if symptoms were not controlled.

Covariate predictors

The following covariates, as shown in Table 9, defined previously were found to be statistically significant in predicting mortality in AD patients with BPSD: AAs (Chi-square (df) = 49.3379 (7), p = <.0001), age (Chi-square (df) = 114.4709 (7), p = <.0001), gender (Chi-square (df) = 41.3692 (7), p = <.0001), acute renal failure (Chi-square (df) = 9.2507 (7), p = 0.0024), cancer (Chi-square (df) = 8.293 (7), p = 0.004), pacemaker presence (Chi-square (df) = 7.7225 (7), p = 0.0055), hypertension (Chi-square (df) = 6.7782 (7), p = 0.0092) and congestive heart failure (Chi-square (df) = 4.7335 (7), p = 0.0296).

Interaction tests were completed among these covariates and none were found. Multicollinearity can be a problem with proportional hazard models (Van den Poel &

Larivière, 2004). The remaining significant covariates were tested using Schoenfeld

residual tests and the duration to death variable, as recommended by Van den Poel &

Larivière (2004). Age and hypertension were found to have potential multicollinearity

issues. However, further correlation tests found no significant impact on the survival

analysis outcome.

Table 9

Mortality Predictions of AD with BPSD and AA use

	Cox Proportional Hazards Significance Tests		
	Chi-Square	df	*p*
Atypical Antipsychotics	49.338	7	<.0001
Age	114.471	7	<.0001
Gender	41.369	7	<.0001
Acute Renal Failure	9.251	7	0.0024
Cancer presence	8.293	7	0.0040
Pacemaker presence	7.723	7	0.0055
Hypertension	6.778	7	0.0092
Congestive Heart Failure	4.734	7	0.0296

Survival Analysis

Atypical antipsychotic use versus non-use

Unadjusted (univariate) analysis

Employing the Kaplan-Meier product-limit survival estimates using log-rank

univariate analysis, there is a significant difference between AA use and non-use over 36

months, (Chi-square (df) = 24.1566 (1), $p = <.0001$), as shown graphically in Figure 9.

Cox Proportional Hazard univariate analysis, concurs with this result, (Chi-square (df) =

48.7367 (1), p = <.0001). The odds of dying over 36 months for AA users is 29.6% less

than non-users (HR = 0.704, 95% CI = [0.638-0.777], $p = <.0001$), without controlling

for other covariates.

Figure 9

Unadjusted Survival Probability without Covariates - AA Users vs. Non-users
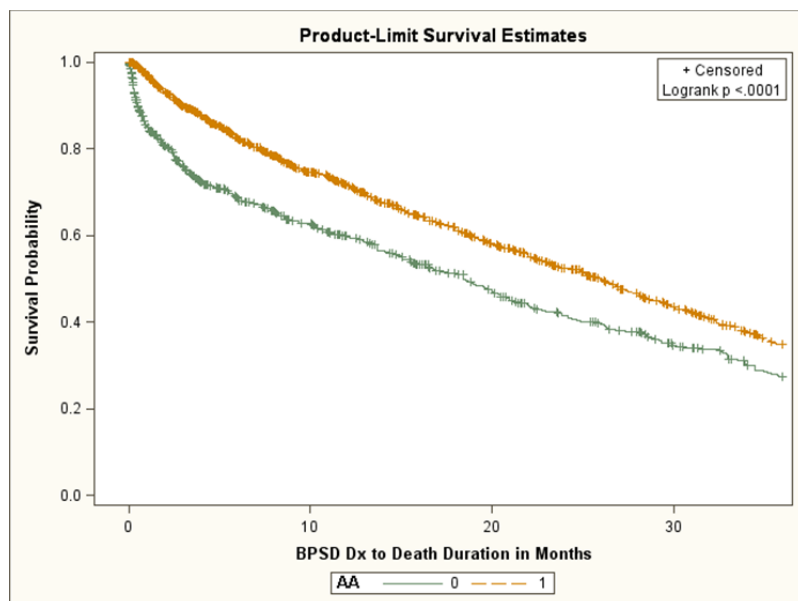
Note: AA = 1: AA user, AA = 0: non-user

Adjusted (multivariate) analysis

Employing Cox Proportional Hazard multivariate analysis and controlling for the significant covariates defined above, the hazard ratio for AA use over non-use improved to 0.699 (HR = 0.699, 95% CI = [0.632-0.772], $p = <.0001$) from 0.704, as shown in Table 10, a hazard ratio difference of .005, or one half of a percent in risk in death.

For every year in increased age over 65 years old, there is a 4.5% increase in risk of death (HR = 1.045, 95% CI = [1.037-1.054], $p = <.0001$). Males are at 40.9% higher risk of death than females (HR = 1.409, 95% CI = [1.269-1.564], $p = <.0001$). Patients with acute renal failure, cancer presence and congestive heart failure are at 19.2%, 20.4% and 13.7% higher risk of death, respectively, (HR = 1.192, 95% CI = [1.064-1.335], $p = 0.0024$), (HR = 1.204, 95% CI = [1.061-1.366], $p = 0.004$) and (HR = 1.137, 95% CI = [1.013-1.277], $p = 0.0296$), respectively. Patients with pacemakers and hypertension are

at 26% and 15.6% lower risk of death, respectively, (HR = 0.74, 95% CI = [0.598-0.915],

p = 0.0055), (HR = 0.844, 95% CI = [0.743-0.959], *p* = 0.0092).

Table 10

Adjusted Survival Probability with Covariates - AA Users vs. Non-users

	Chi-Square	df	*p*	Hazard Ratio	Confidence Interval	
					Upper	Lower
Atypical Antipsychotics	49.338	7	<.0001	0.699	0.632	0.772
Age	114.471	7	<.0001	1.045	1.037	1.054
Gender	41.369	7	<.0001	1.409	1.269	1.564
Acute renal failure	9.251	7	0.0024	1.192	1.064	1.335
Cancer presence	8.293	7	0.0040	1.204	1.061	1.366
Pacemaker presence	7.723	7	0.0055	0.740	0.598	0.915
Hypertension	6.778	7	0.0092	0.844	0.743	0.959
Congestive heart failure	4.734	7	0.0296	1.137	1.013	1.277

Medication analysis

As indicated in Table 5 above, nearly a third, 31%, of AA users were prescribed

more than one AA. Therefore, the analysis of medications will not focus simply on single

medications, but analyze single medications in context of all medication permutations,

i.e., comparisons of combinations of medications, in addition to single medications.

Medication mix

A combination of AAs medications, which could be sequential or simultaneous

use, shows a lower risk for death than use of just one AA, as indicated in the Kaplan-

Meier product-limit survival estimates using log-rank analysis in Figure 10 (Chi-square

(df) = 45.454 (1), *p* = <.0001).

Figure 10

Number of AA's Prescribed Over Study Period

One AA versus Greater or Equal Two AAs versus No AAs
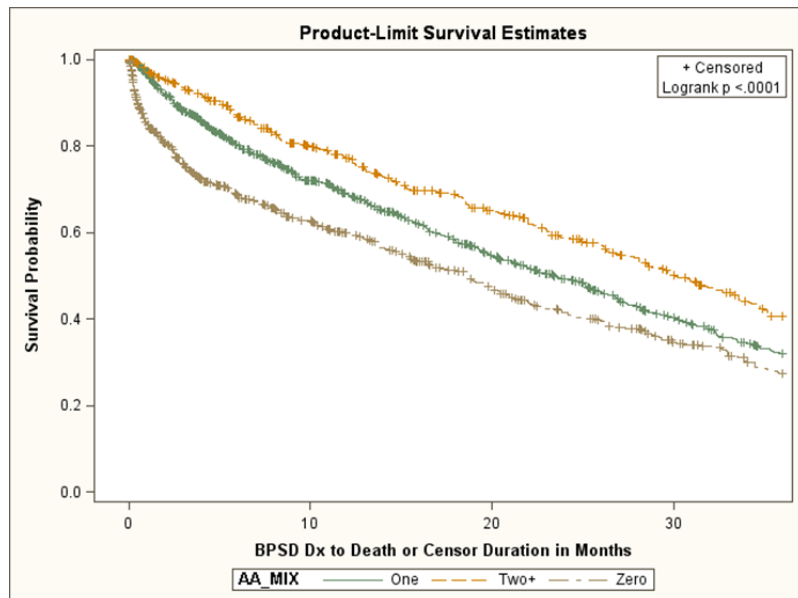
A Cox proportional hazards analysis reveals that a combination of two or more AA medications has a 40.9% lower risk for death versus a 25% lower risk for death for only one AA medication when both are compared to zero (non-use) or no AA medication, as shown in Table 11, (HR = 0.75, 95% CI = [0.664-0.846], p = <.0001), (HR = 0.591, 95% CI = [0.508-0.689], p = <.0001), respectively.

Table 11

Number of AA's Prescribed Over Study Period

One AA versus Greater or Equal Two AAs versus No AAs

Number of AAs Prescribed	Chi-Square	df	p	Hazard Ratio	Confidence Interval	
One	21.825	1	<.0001	0.750	0.664	0.846
Two or more	45.454	1	<.0001	0.591	0.508	0.689

When investigating the specific AA medications by generic name, risperidone shows the lowest hazard risk for death for single AA medications, (HR = 0.682, 95% CI = [0.579-0.803], p = <.0001), when compared to non-use of AAs, as indicated in Table 12. The combination of olanzapine and quetiapine shows the lowest risk of the combination of two medications, when compared to non-use of AAs, (HR = 0.625, 95% CI = [0.481-0.811], p = 0.0004).

Table 12

Combination of AA's Prescribed Over Study Period

Single, Two AAs and All AAs

	Chi-Square	df	*p*	Hazard Ratio	Confidence Interval	
					Upper	Lower
Single Medications						
Risperidone	21.184	1	<.0001	0.682	0.579	0.803
Olanzapine	7.595	1	0.0059	0.752	0.614	0.921
Quetiapine	0.082	1	0.7753	1.023	0.875	1.197
Two Medications						
Olanzapine & quetiapine	12.497	1	0.0004	0.625	0.481	0.811
Risperidone & quetiapine	8.982	1	0.0027	0.711	0.569	0.889
Risperidone & olanzapine	3.921	1	0.0477	0.762	0.583	0.997
Three Medications						
All AA's	19.657	1	<.0001	0.568	0.442	0.729

Medication dosage

Is dosing greater than the minimum dose associated with greater mortality? A Kaplan-Meier product limit survival estimate analysis indicates that it is not. After an analysis of multiple dosing groups, a natural break between a dosing strength of one and a dose of greater than one was indicated. Therefore, dosing strength was divided into two groups: the first group are those cases where dosing was the standard minimum of 1 or under, and the second group are those cases where dosing was greater than 1. Both

groups were found to have lower risk when compared to non-users, as shown in Figure 11.

Figure 11

Dose Strength

Less than or Equal to One and Greater than 1 versus AA Non-Users
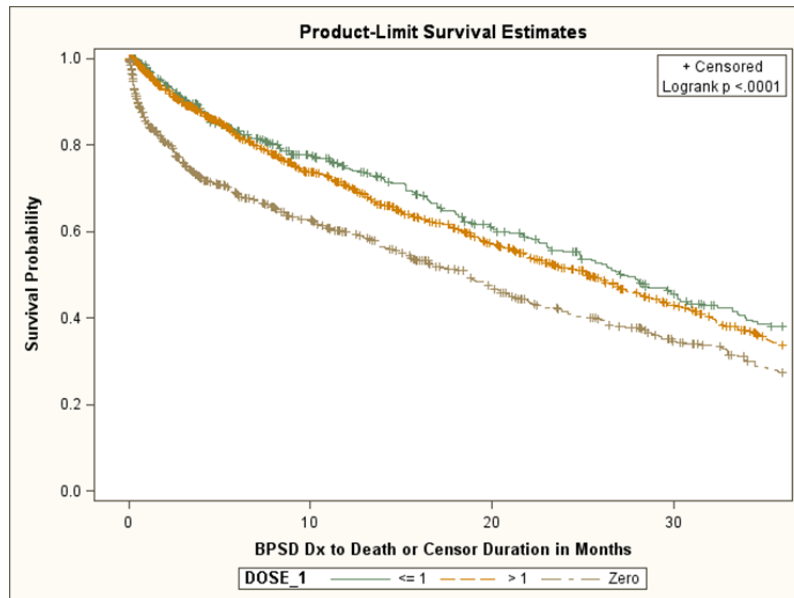
An AA dosage less or equal to 1 is associated with 35.5% lower risk when compared non-use and a dosage greater than 1 is associated with a 27.6% lower risk, (HR = 0.645, 95% CI = [0.551-0.755], p = <.0001), (HR = 0.724, 95% CI = [0.652-0.805], p = <.0001), respectively. A Cox proportional hazards test between the two dosing groups on their own was completed and the difference was found to be insignificant (HR = 1.123, 95% CI = [0.957-1.319], p = 0.1557).

Dose frequency & changes

Does daily usage, as opposed to as-needed usage for symptom control, present higher mortality risks for AA users? Cox proportional hazard analysis found the

difference to be insignificant when compared to each other for mortality risk, daily usage (HR = 1.01, 95% CI = [0.809-1.262], p = 0.9268), and as-needed usage (HR = 0.99, 95% CI = [0.792-1.236], p = 0.9268).

Does allowing a patient to increase their dose increase the risk of death when compared to not allowing a patient to increase their dose based on symptom management needs? Cox proportional hazard analysis found the difference to be insignificant when compared to each other for mortality risk, allowing for an increase (HR = 1.078, 95% CI = [0.701-1.66], p = 0.7313), and not allowing for an increase (HR = 0.927, 95% CI = [0.602-1.427], p = 0.7313).

One-time prescriptions

As discussed above, there is a large group of AA users who received only one prescription of AAs. What is the mortality risk for this group when compared to those who received more than one prescription of AAs, or those who were not AA users? An analysis using the Kaplan-Meier survival-estimation methodology indicates that those who received only one prescription of AAs are at higher risk of death, as shown in Figure 12.

Figure 12

One-time AA user Mortality Risk

One-time AA user versus more than one time AA user versus non-AA users
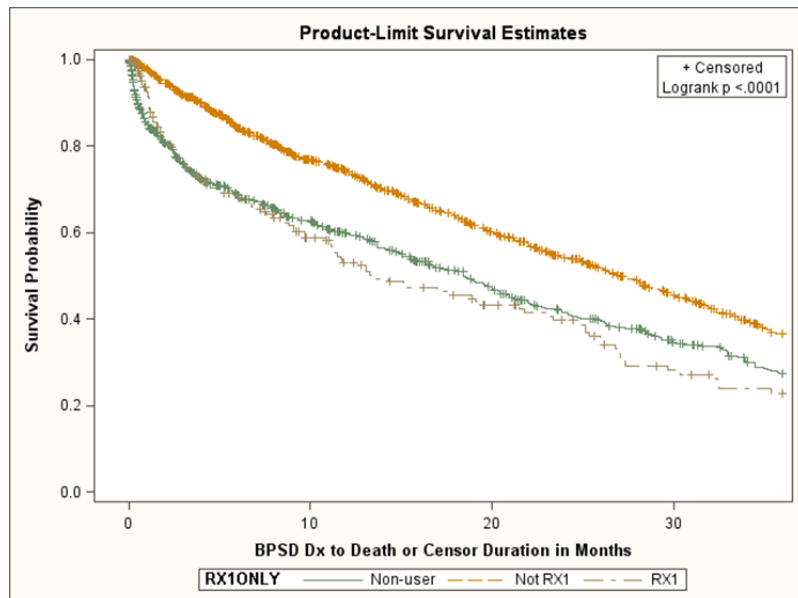
Cox proportional hazard analysis found the difference to be significant for one-time prescription AA users when compared to more than one-time prescription users for mortality risk: one-time prescription users (HR = 1.428, 95% CI = [1.121-1.818], p = 0.0039), and more than one-time prescription users (HR = 0.7, 95% CI = [0.55-0.892], p = 0.0039). One time prescription AA users are at 42.8% higher risk for death than more than one time prescriptions users of AAs. Additionally, non-AA users are at 39.8% lower risk of dying when compared to one-time users (HR = 0.602, 95% CI = [0.492-0.738], p = <.0001).

Compliance

Using the MPR as an indicator of compliance, does compliance indicate higher or lower risk for death? As discussed previously, there is a natural break between a MPR of

less than 1 and a MPR equal to one, with the proportion of deaths between the groups not significant (Chi-square (df) = 3.2880 (1), p = 0.0698). An analysis using the Kaplan-Meier survival-estimation methodology indicates those with an MPR equal to 1 are at higher risk of death when compared to patients with an MPR less than 1, but still lower than non-users, as shown in Figure 13.

Figure 13

MPR Risk by Group

MPR score less than 1 vs. equal 1 vs. one-time prescription
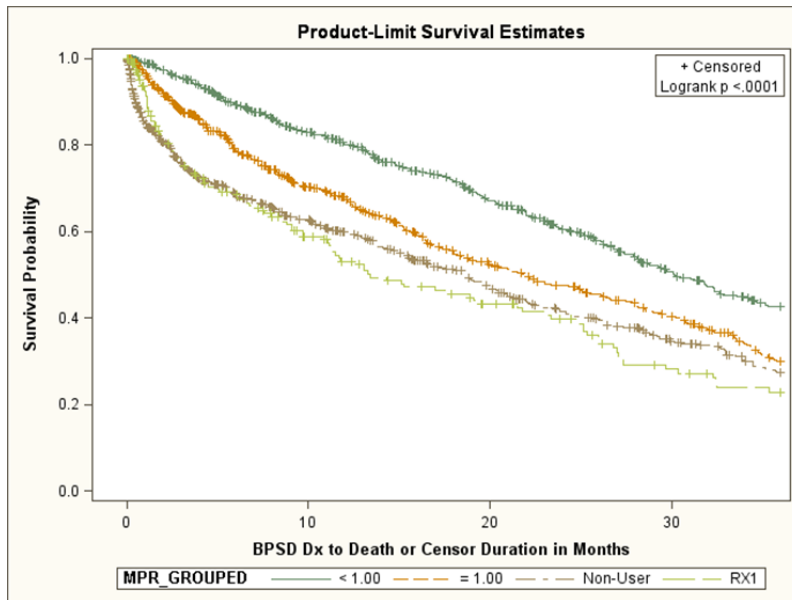
Cox proportional hazard analysis found the difference for mortality risk to be significant for those with MPR less than one when compared to those equal to one, (HR = 0.682, 95% CI = [0.59-0.79], p = <.0001), and MPR subgroup one-time prescription (HR = 0.498, 95% CI = [0.401-0.619], p = <.0001). Those with MPR scores less than 1 are at 31.8% lower risk for death than those patients with MPR scores equal to 1 and 50.2% lower risk for death than those with one-time prescriptions.

Discussion

Despite the FDAHA finding of a slightly higher mortality risk with the use of AAs with dementia patients, AAs remain a widely used medication because AAs are the only pharmacological tool available to ameliorate BPSD. This is the first large community pair match controlled observational study to analyze the association of mortality and AA use based on a diagnosis of AD and BPSD, in addition to an analysis of correlated medication factors. Previous observational studies have analyzed AD with AA usage in acute care nursing home and long term care facilities or analyzed all dementias. No observational studies have analyzed correlated medication frequency, dosage levels and compliance factors.

Contrary to the small RCT studies that formed the basis for the FDAHA and some all dementia observational studies, this study provides evidence that the mortality risk for the use of AAs for AD and BPSD is lower than non-use of AAs. This finding is valid for unadjusted and adjusted comorbidities. Controlling for age, gender and several heart related comorbidities and conditions, i.e., congestive heart failure, hypertension and the presence of a pacemaker, in addition to renal failure and cancer comorbidities, provides only the smallest of margins in narrowed additional risk, one half of a percent, when comparing adjusted results versus non-adjusted results.

The finding of lower risk for death for AA users versus non-users is consistent with two observational mortality studies of dementia patients using AAs (Simoni-Wastila et al., 2009; Suh & Shah, 2005). The Simoni-Wastila, et al. (2009) study found a hazard ratio with their dementia patient subgroup, controlling for comorbidities, of 0.78, versus this study's hazard ratio of 0.699. Simoni-Wastila, et al. (2009) was a retrospective

observational investigation of deaths of Medicare patients, with and without any form of

dementia, in long term care facilities taking AAs over a 3 year period. The Suh & Shah

(2005) study indicated a relative risk of 1.288 of death for non-users within the study's

AD subgroup. Suh & Shah (2005) was a Korean quasi-experimental prospective study

with 273 hospital subjects with AD and vascular dementia over a 3 month period, with a

1 year follow-up.

However, this study's finding of lower risks for death for atypical antipsychotic

users runs counter to three influential meta analyses of RCTs of mortality with dementia

patients and atypical antipsychotic (C. Ballard, Creese, Corbett, & Aarsland, 2010;

Kryzhanovskaya, et al., 2006; L. Schneider, et al., 2005), and the largest case controlled

observational mortality study investigating mortality with dementia patients using

atypical and conventional antipsychotics (Gill, et al., 2007). These studies found atypical

antipsychotic users are at 4% to 15% greater risk of dying than non-users over the course

of the 90 to 180 day periods of all of these studies. One of the meta analyses, (L.

Schneider, et al., 2005), was part of the FDA analyses which lead to the FDAHA on use

of atypical antipsychotics with dementia.

The significant covariates in this study are consistent with the previous dementia

and AA mortality studies. Male gender and advancing age are almost universally found to

be significant predictors for death with dementia, in particular with AD, as well as AD

with use of AAs (Bonsignore & Heun, 2003; Kamble, Chen, Sherer, & Aparasu, 2009;

Liperoti, et al., 2009; Simoni-Wastila, et al., 2009). Bonsignore and Heun (2003) found

the only significant predictor of increased mortality, outside of advancing severity of AD,

was the age at first AD diagnosis. Several AD and AA studies have shown consistent

results with this study that males are at higher risk for death (Simoni-Wastila, et al., 2009; Suh & Shah, 2005; Sultzer, et al., 2008; Wang, et al., 2005). Acute renal failure and cancer in this study were also found to increase risk for death with AA use. The finding for renal failure has been reproduced in one study (Wang, et al., 2005), but no other studies were found to reinforce the acute renal failure finding. That being said, pharmacology textbooks and guides warn against using AAs with patients with impaired renal clearance given that AAs are cleared from the body through the kidneys (Keltner & Folks, 2005).

In the adjusted results, this study found several heart related covariates to be predictive of mortality with AD patients with BPSD using AAs: congestive heart failure, which increased risk, in addition to hypertension and the presence of a pacemaker, both of which lowered risk. This is consistent with many AD and dementia studies and the use of AAs, where heart related covariates are often referred to as cardiovascular risk factors (CVRF). Some studies showed evidence that non-users were at lower risk for death when compared with atypical antipsychotic users with congestive heart failure (Suh & Shah, 2005; Wang, et al., 2005). A meta-analysis found selected CVRFs to be factors that would improve survival rates for atypical antipsychotic users, as found in this study for hypertension, but would not alter the risk differential with non-users (Kryzhanovskaya, et al., 2006).

The inclusion of the presence of a pacemaker covariate in this study, in addition to the significance of it being a predictive covariate, is unique. There were no other studies found that include this as a covariate. Because a number of studies have shown all classes of antipsychotics prolong cardiac QT intervals and possibly lead to higher

mortality (Reilly, Ayis, Ferrier, Jones, & Thomas, 2000; Stollberger, Huber, & Finsterer, 2005), the inclusion of a pacemaker covariate was included to test the hypothesis that pacemakers reduce mortality. This study found AA users with the presence of pacemakers were at 26% lower risk of death thus confirming the hypothesis using this study's sample.

A number of studies have found an association between cerebrovascular accidents (CVAs) and use of AAs with AD patients. This study found no predictive association between CVAs as a comorbidity covariate and the use of AAs. Previous studies of AD subjects have shown higher risk of CVAs with AA use. An influential RCT investigating atypical antipsychotic with Alzheimer's disease patients showed an increase in the incidence of CVAs (Brodaty et al., 2005) with AA use and subsequent pharmaceutical company clinical trials disclosed a threefold increase in the incidence of CVAs (Suh & Shah, 2005). As stated previously, the FDAHA made specific reference to the higher risk association between CVA's the use of AAs with dementia patients. However, this study could not find a significant covariate combination where CVAs were a significant predictor of mortality risk with AAs and AD with BPSD

This study is unique in providing risk comparison evidence related to multiple medication usage factors: number of medications, as well as medication dosage strength, frequency and flexibility. In the case of one medication versus multiple medications, this study found patients taking more than one medication were at lower risk for death than those who were taking just one medication. There are possibly two reasons for this phenomenon. First, the first medication prescribed may not be the most efficacious medication for a patient and a switch to a second, or even a third, medication may

provide greater efficacy. Second, there are instances where one medication may be efficacious in the daytime and another may be more efficacious in the evening. There are instances of cases in the study where patients took risperidone in the daytime and olanzapine in the evening, which does have a greater sedative effect. An influential RCT, one that was included in the FDAHA review, documented fewer adverse effects from cases where patients had used more than one medication due to being switched medications (L. Schneider, et al., 2005). Other studies have shown no impact on death rates or acuity (C. G. Ballard & Waite, 2006; Bullock, 2005; Carson, et al., 2006; Jeste, et al., 2005; Lee et al., 2004) when comparing single medication to more than one medication usage.

It was determined in this study that the recommended prescribed dosage, or lower than the recommended dosage, does not significantly change the risk of death when compared with dosages of greater than the recommended minimum. However, dosage strength of 1 or less versus dosage strength of greater than 1 shows a slightly lower risk when compared to non-user risk for mortality, 35.5% versus 27.6%, respectively. Dosage strength is a decision made by the prescribing physician based on a number of factors, not limited to, age, gender, comorbidity profile, patient polypharmacy and severity of symptoms. Dosage strength is assumed to increase appropriately with symptom severity. Therefore, it might be reasonable to assume if there is no difference in risk for death based on increase in dosage, patients are receiving the appropriate dose based on their acuity. The evidence related to dosage strength has been inclusive or mixed. Many of the RCTs have either restricted increases in dosage based on patient safety concerns and/or lack of study duration (L. Schneider, et al., 2005). All but one of the most influential

RCTs has been 12 weeks or less (C. Ballard, et al., 2010; Kryzhanovskaya, et al., 2006; L. Schneider, et al., 2005), which makes it difficult to test different dosage levels with a medication that needs to be titrated slowly according to psychotropic medication guidelines (Keltner & Folks, 2005; Lehne, 2004). In a broad pharmaceutical meta-analysis study, which investigated psychotropic medications used in a number of different neurological pathologies, the lowest dosages of risperidone were associated with higher mortality in dementia patients, while the highest dosages of quetiapine and olanzapine were associated with higher mortality in dementia patients (Stollberger, et al., 2005). These studies suggest that dosage strength cannot be analyzed across all medications as a group, but must be considered individually based on evidence.

Current guidance in pharmacology textbooks and clinical guidelines recommend daily dosing and slow titration for increases in dosing (Keltner & Folks, 2005; Lehne, 2004). This study indicates 85% of cases were given prescriptions directing that the patient should not deviate from a specific daily intake and a specific daily dose. The remaining 15% of cases allowed the patient to deviate from the strict daily dosing such that they could take the medication as needed during the day or evening. Additionally, 3% of the cases indicated there was some flexibility with the dose strength versus 97% with no flexibility in changing the dose strength. The assumption with the flexible directions is that the patient has gone through the initial dosing period and is given some flexibility after they have reached the appropriate titration level. This study indicates there is no difference in mortality risk for the flexible directions when compared with the no deviation directions. It suggests flexibility where the prescribing primary care provider

believes it is appropriate does not place the patient at additional risk may be the best strategy. There are no comparable studies to compare this finding known to this author.

The death rate with only a one-time prescription is very high, with 98% of the deaths occurring in the first three months after starting the prescription. The risk for death for one-time prescription patients is higher than even that for non-users. This finding is consistent with another large observational case controlled study completed within the Canadian health system. In that study, new use of AAs was associated with a statistically significant higher risk for death (Gill, et al., 2007), with a hazard ratio of 1.31. A deeper analysis in this study indicates one-time prescription users are older, more male and have significantly higher Charlson Morbidity Index scores, and higher incidence of CVRFs and CVAs. A hypothesis could be proposed that this group is being given AAs for palliative purposes with death expected imminently. However, this group has a lower incidence of being under hospice or SNF care. If the medication is being given for palliative purposes, it is being given within home care. There are no studies known to this author that test this hypothesis.

It is an interesting finding in this study that the medication compliance metric, the MPR, indicates that those patients with MPR less than one have lower risk for mortality than those that are fully compliant. Based on evidence this may not be all that surprising. A number of the RCT studies indicated there are a large percentage of patients who would go off and on the medication due to side effect issues (Brodaty, et al., 2005; L. Schneider et al., 2006; Street, et al., 2000). These subjects were thrown out of the studies. The only study found that utilized the MPR metric with AAs was with schizophrenia patients and was an observational study testing hospital utilization (Al-Zakwani, et al.,

2003). Subjects in the schizophrenia study were thrown out of the study if they switched

medications. However, it has been documented in this study to be nearly a third, 31%, of

the cases, switched medications. Therefore, support from published evidence is lacking.

Medical decision making and study results

The stated purpose of this study is to provide detailed survival, hazard and

probability information on mortality risk for clinicians treating patients with AD and

BPSD. The probability information which can be derived from this study demonstrates

which conditions place a patient at higher risk of death, controlling for use of AAs and

common chronic diseases. The target for the information in this study are clinicians who

need risk assessment data in order to make more informed decisions on the prescribing of

AAs for their patients suffering from AD and BPSD.

The current state of clinical decision making on the use AA use with AD with

BPSD patients is limited to a very small set of odds ratios published by various studies,

mostly the RCTs with limited timeframes of less than 6 months. These studies have

indicated that there appears to be higher mortality probability related to cardiovascular

risk factors and cerebrovascular accidents. However, the specificity in terms of odds

ratios does not provide deep granularity. Due to the high mortality rate in this population,

in particular in advanced ages and acuity levels, the risks are elevated when making a

decision related to AA treatment for BPSD symptoms with AD patients.

Without a standardized medical decision process, including decision trees, to aid

the clinician in making a safer, and hopefully more efficacious, decision about the use of

AAs as a treatment option, the clinician would be left with the ad hoc decision making

approach. This would be a less informed and potentially more risky and less reliable

decision process. Additionally, with a decision tree process with evidence based probabilities from studies like this one, the clinician could have objective risk assessment information which could be discussed with family and caregivers. This assumes the patient is too psychotic or cognitively impaired from their dementia and/or BPSD to be a key decision maker. With more objective risk assessment tools available, the decision for the clinician and family involves less opinion, personal and professional experience, and incorporates more historical information about conditions that are similar to the patients' symptoms.

Conclusion

This study provides evidence that AD patients with BPSD taking AAs have lower risk for death than non-users when controlling for cardiovascular risk factors, renal failure and cancer. Mortality risk can be further reduced by careful medication management, which involves a longer term, non-one time prescriptions strategy with flexible medication choice, dose strength and frequency based on patient conditions and needs. In addition, pacemakers may be protective for patients with heart issues and further research may be warranted.

Significance

This is the first study of community dwelling AD patients with BPSD to study the mortality risk of the use of AAs from the time of first diagnosis of BPSD, in addition, it is the first study of sufficient duration to analyze various factors in medication management. This study finds new evidence that careful AA medication management of pharmacodynamics may be helpful in significantly lowering mortality risk. Rather than a binary decision of whether to use AA medications or not because of higher mortality risk to this population, this study provides new evidence that AA medications can be managed for lower mortality duration.

Additionally, the duration of previous RCT safety and efficacy studies have been too short to investigate flexibility in medication management over the longer term for mortality risk. Previous observational studies have not investigated BPSD duration to death and medication management beyond polypharmacy. Therefore, this study's findings have indicated that lower mortality risk may be a product of time and trial in finding the right pharmacodynamics for AD patients with BPSD.

Finally, the finding that pacemakers may lower risk opens a new avenue of research to investigate the relationship with QT elongation and pacemakers, and the use of AAs with dementia patients. This study did not measure QT elongation in subjects and therefore cannot speculate about the protective effects of pacemakers in this group of AD patients with BPSD using AAs. However, previous evidence of AA use with QT interval elongation has been a topic of speculation that this may be a factor in higher mortality among dementia patients taking AAs. This study's evidence points to the need for more investigation into the possible protective effects of pacemakers and AA use among AD patients with BPSD. A portion of patients with heart related comorbidities that have been previously precluded from AA treatment because of concerns of higher mortality risk may be included as treatment candidates in the future if they have pacemakers. Further research needs to be completed to test this hypothesis.

Nursing Implications

A large number of nurse practitioners (NP) are utilized in home health and nursing homes as the primary healthcare provider and medication prescriber. Within KP, nurse practitioners are the majority of home health care providers. This is also true in a number of skilled nursing facilities KP contracts to provide skilled nursing care. After initial diagnosis and a prescription, NPs are generally the prescriber for AAs longer term, as well as being, in a minority of case, the first prescriber for AAs. With the findings this study provides, NPs will have more evidence-based data to help them, the patients, their patients' families and caregivers, in making safer and more intelligent decisions about possible AA treatment for AD with BPSD. In addition, this study provides non-NP nurses

with information that they may communicate to PCPs related to possible treatment for patients that are under their care.

Study Limitations

Observational study

This study is a retrospective observational study: these studies are known to have bias and confounding issues (Austin, et al., 2007; D'Agostino, 1998). The objective of the study's process of propensity score matching for case control selection was to mitigate those issues. Sensitivity analysis was not executed to enumerate potential remaining confounding issues after the PSM process. It was beyond the skill set of this author and available statistician consultants to properly execute a sensitivity analysis to elucidate any issues related to the case control matching process.

Time to death duration

The time to death duration in this study was from first BPSD diagnosis to death and not the start of AA treatment to death. Therefore, it's generalizability to AA mortality specifically is limited. The primary objective of the study is to understand the broader context of the use of AAs within the context of the symptom arc of BPSD.

Age constraint

This study was restricted to adults 65 and over in age. In the original cohort database, patients with early onset dementia, as low as 50 years old, were included. Therefore, the study is not inclusive of all patients with a diagnosis of BPSD.

Demographic sampling skew

The study's original cohort sample reflects the patient mix of a large HMO and cannot necessarily be generalized to the broader population because of the socio-economic profile of the HMO. Low-income segments of the population who cannot afford insurance premiums, or who may not work for companies or governmental entities

that provide health insurance may be underrepresented; as well as very high income subpopulations that do not normally join HMOs. Therefore, the study may have some generalizability issues based on a socioeconomic bias.

Demographics beyond age and sex

Extensive demographics beyond age and sex were not available for this study. Therefore, controlling for possible non-clinical covariates such as education, marital status, race, ethnicity, poverty, urban versus suburban and rural locations were not possible. Other similar comparative studies, such as Simoni-Wasilla et al (2009) included such covariates.

Comorbidity covariates based on last recordings

In order to overcome some of the confounding and/or bias related issues to a start of diagnosis based study versus a start of treatment based study, the case matching in this study was based on last comorbidities covariates, where acuity levels are highest. The objective of utilizing the last covariates was to mitigate the bias and confounding related to a first BPSD diagnosis start time. Numerous studies have confirmed that AAs as a treatment for BPSD and psychosis is a very late stage phenomenon of dementia (Bowen et al., 1996; Cohen-Mansfield, 1986; Eustace et al., 2002; Gilley, et al., 2004; Keene, et al., 2001; Mega, et al., 1996; Okura, et al., 2010; Petrovic, et al., 2007). Therefore, the decision to base case matching on last diagnoses is arguably valid up to a certain point, because one could argue that case control matching acuity comparisons should have been set at BPSD start or at AA use start.

Measures analysis

The measures in this study are based on administrative data and do not include biomarkers and cognitive score levels of the subjects, such as MOCA and/or MMSE scores. Therefore, finer detail on the severity of a subject's dementia cannot be ascertained based on the simple diagnosis data utilized in the study. This is a mortality study and not an efficacy study. As an example the study does not measure if psychosis improvements occurred after AA usage occurred

Treatment implementation reliability

Along with observed medication ingestion being a treatment reliability issue, dosage and as-needed dosing may also be a reliability issue. It is not known what the compliance rate of the ingestion is of the AAs amongst the subjects studied. It is not known if they took the medication at all, once only, or on an as needed basis, or timing of the dosing and additional dosages beyond the recommended dosage. The running assumption in the study is that the subjects were fully compliant in their taking of the medications based on the prescribing care provider's instructions, the data source for the analysis, including frequency, dosing levels and timing of ingestion. Finally, the study did not make any distinction between liquid, tablet or intramuscular routes. Dosing accuracy is based on the recorded number of number of doses in a prescription divided by the number of doses instructed to be taken on each day.

First time prescriptions

An inclusion criterion in this study is that only patients with a first prescription during the study period be included. The data inclusion and cleaning process made all efforts to determine this based on KP records. However, there may be an undetermined

number of subjects who were not first time AA users because they had been prescribed

AAs outside of KP or were AA users prior to 2001, the earliest that AA records were

available for this study.

Future research questions

As stated previously, more research needs to be completed on a finding in this study that pacemakers provide lower risk for AD patients taking AA medication for their BPSD. What is the protective effect of pacemakers? Because previous studies have found QT elongation occurs more frequently with patients taking AAs, what exactly is the protective effect of pacemakers physiologically?

What is the clinical profile of AA users who have a history of longer survival with the use of this class of medications? This study did not provide data related to cause of death. This study and other studies have provided evidence of early deaths with this population. But we don't really know why. This study effectively elucidates two different clinical histories, one with relatively short duration to death, one to a few months, and another with a long history with the use of the medication, averaging over a year. Why is there a very large number of patients that die early after first diagnosis of BPSD and the first and only prescriptions of AAs? What is the pathophysiology of these early deaths and how much of it is related to AD and/or BPSD? Is it simply that these patients were close to death, and BPSD is only a biomarker for impending death?

One of the unknowns in an observational medication use study is the true dosing and frequency history of the patients being studied. RCTs control this variable reasonably well, especially in long term care settings. However, observational studies generally lack this information. Studies, like this study, can only use the prescriber's instructions as a proxy for use. It would be helpful if studies utilizing prescription diaries were executed and published related to AAs and dementia. Therefore, research questions surrounding actual use could be more accurately investigated. As an example, controversy remains as

to what strategy is better for treatment, as needed, or on a continuous basis. Does continuous use with no gaps in use provide lower risk or higher risk than gaps in use?

Finally, the effect of other medications with AAs and dementia has not been studied thoroughly. One of the comparable studies to this study used the binary condition of polypharmacy as a covariate in its analysis, but did not go any deeper (Simoni-Wastila, et al., 2009). Available research on polypharmacy is largely focused on schizophrenia, and not AD. There may be confounders in the use of medications. Therefore, a clinically relevant and meaningful research question would be: what medications in a polypharmacy environment create lower or higher risk conditions when used in combination with AAs?

Appendix

Study Length Comparisons

The length of this survival study at 3 years using patient histories over an 8 year period is longer than the only previous case controlled observational mortality study, a 6 year Canadian health system study comparing AA use against non-use, which analyzed mortality over 180 days with 1 year follow-up (Gill, et al., 2007). This study is also longer than two other significant non-case controlled mortality studies with AA usage: one observational, with 2,363 Medicare subjects over a 3 year period (Simoni-Wastila, et al., 2009); and one Korean quasi-experimental study with 273 hospital subjects over a 3 month period, with a 1 year follow-up (Suh & Shah, 2005)[1]. Finally, this study is substantially longer than any previous RCT according to three key RCT meta-analyses, which ran 30 to 180 days (C. Ballard, et al., 2010; Kryzhanovskaya, et al., 2006; L. Schneider, et al., 2005).

Internal Validity and Reliability

The following discussion addresses the issue related to the relationship between the independent and dependent variables in the study and the threats to internal validity:

Selection

In this retrospective study, selection to the study is very strongly related to diagnosis accuracy. Patients are not selected to be part of the study unless they receive diagnoses of AD with BPSD. If there are issues with the diagnoses of patients, then there is a weakening effect of the selection process.

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[1] It should be noted the Suh & Shah (2005) study was funded by the pharmaceutical company Janssen, the maker of the AA risperidone

Maturation

Maturation may be an issue in this study, but it is an unknown issue, yet to be discovered. Maturation addresses the issue of naturally occurring changes in patients that are not addressed in the study design (Polit & Beck, 2004). The use of AAs may accelerate that deterioration in a way that is not yet understood.

Instrumentation validity

The primary threat to construct validity is one that is shared with many retrospective studies based purely on administrative data: mono-method bias. The most important of the primary criteria for sample selection is a diagnosis record. Other criteria could have included cognitive scores, such as the Mini-Mental Status Exam (MMSE) or Montreal Cognitive Assessment (MOCA), and neuropsychiatric testing. But those criteria are not part of this study.

Procedure

The intervention procedure in this study is the taking of AAs. This study is a retrospective study and therefore there are no prospective experimental intervention procedures to be disclosed. However, retrospectively, it is important to note that the intervention procedure of this study is tracked indirectly, through the dispensing of the medication and not the observed ingestion of the medication, or a recording of the time and dose of the medication use.

Power analysis

A power analysis was executed prior to the start of the study on the estimated smallest possible sample the study could have been utilized, 1,800 patients. These patients comprised only those dementia patients with an Alzheimer's disease and BPSD

diagnoses taking AAs who expired. Using a Cox regression log hazard ratio on a

covariate with a standard deviation of 0.5000 and based on a sample of 1,800

observations, the study's sample achieves greater than 80% power at a 0.05000

significance level to detect a regression coefficient between 0.1600 and 0.1700. The

sample size was adjusted since a multiple regression of the variable of interest on the

other covariates in the Cox regression is expected to have an R-Squared of 0.1000. The

very low regression co-efficient and R-Squared is based on the expectation that the case

control methodology, propensity score matching, will greatly reduce the statistical effects

of covariates. The sample size was adjusted for an anticipated event rate of 0.7500.

The significant power analysis results of the smaller sample indicated further

power analysis was not needed. The power analysis results are shown in Table 13.

Table 13

Power Analysis

Power	Sample Size (N)	Reg. Coef. (B)	S.D. of X1 (SD)	Event Rate (P)	R-Squared X1 vs Other X's (R2)	Two-Sided Alpha	Beta
0.41406	1800	0.1000	0.5000	0.7500	0.1000	0.05	0.58594
0.48292	1800	0.1100	0.5000	0.7500	0.1000	0.05	0.51708
0.55229	1800	0.1200	0.5000	0.7500	0.1000	0.05	0.44771
0.62010	1800	0.1300	0.5000	0.7500	0.1000	0.05	0.37990
0.68439	1800	0.1400	0.5000	0.7500	0.1000	0.05	0.31561
0.74354	1800	0.1500	0.5000	0.7500	0.1000	0.05	0.25646
0.79633	1800	0.1600	0.5000	0.7500	0.1000	0.05	0.20367
0.84204	1800	0.1700	0.5000	0.7500	0.1000	0.05	0.15796
0.88043	1800	0.1800	0.5000	0.7500	0.1000	0.05	0.11957
0.91172	1800	0.1900	0.5000	0.7500	0.1000	0.05	0.08828
0.93646	1800	0.2000	0.5000	0.7500	0.1000	0.05	0.06354
0.95544	1800	0.2100	0.5000	0.7500	0.1000	0.05	0.04456
0.96955	1800	0.2200	0.5000	0.7500	0.1000	0.05	0.03045
0.97975	1800	0.2300	0.5000	0.7500	0.1000	0.05	0.02025
0.98689	1800	0.2400	0.5000	0.7500	0.1000	0.05	0.01311
0.99174	1800	0.2500	0.5000	0.7500	0.1000	0.05	0.00826

Table Definitions:

Power is the probability of rejecting a false null hypothesis. It should be close to one.

N is the size of the sample drawn from the population.

B is the size of the regression coefficient to be detected

SD is the standard deviation of X1.

P is the event rate.

R2 is the R-squared achieved when X1 is regressed on the other covariates.

Alpha is the probability of rejecting a true null hypothesis.

Beta is the probability of accepting a false null hypothesis.

Censoring Distribution

The censoring distribution is shown in Figure 14 and Table 14. The group *Died and Uncensored*, in the color orange in Figure 14, represents the expired cases before the end of the study. The *Live and Censored* group, in the color brown, represents those cases where there is no death record and whose last utilization represents the endpoint of the duration or the censor point. The censor point could be before or after the 36 month end of the study. If the censor point is after the 36 months, all of the censor points are marked at 36 months. The third group, *Died and Censored*, in the color green, are those with a death record after the 36 month end of the study and censored. Therefore, the vertical graph bar at the 36th month represents two groups of censored subjects, those who lived and those who died beyond the 36 month period of the study.

Figure 14

Distribution of Durations – Died, Living and Censored
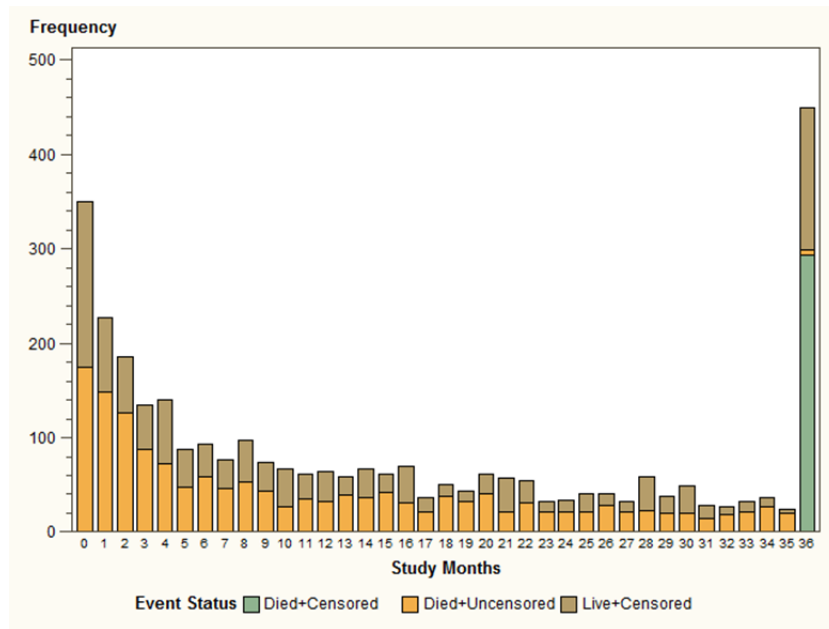
As shown in Table 14, out of the total study sample of 3,140 subjects, 1,575 subjects, or 50% of the study sample, died during the study, 293 subjects, or 9% of the study sample, died after the study, uncensored and censored respectively, while 1,272 subjects, or 41% of the study sample, remained living during the length of the study, all censored.

Table 14

Distribution of Death, Living and Censoring over 36 month Study Period

Duration to death (months)	During 36 mo. Study		After 36 mo. Study		All Subjects	
	N	% of group	N	% of group	N	% of group
Died & uncensored	1,575	58%	0	0%	1,575	50%
Died & censored	0	0%	293	66%	293	9%
Died subtotal	1,575	58%	293	66%	1,868	59%
Living & censored	1,122	42%	150	34%	1,272	41%
Total	2,697	100%	443	100%	3,140	100%

Dementia ICD9 Codes

The ICD-9 codes for Alzheimer's disease:
331.0:   Alzheimer's disease

The ICD-9 codes for BPSD:
290.12:   Presenile dementia with delusional features
290.13:   Presenile dementia with depressive features
290.20:   Senile dementia with delusional features
290.21:   Senile dementia with depressive features
294.11:   Dementia in other conditions classified elsewhere with behavioral disturbance

Propensity Score Matching Covariate Probabilities

Table 15

Odds Ratios of Log Regression to Predict AA Use

Variable	Odds Ratio	Coefficient	Probability
Sex	1.175	0.1611	0.0277
Age	0.98	-0.0203	0.0002
Myocardial infarction	0.994	-0.0065	0.9441
Congestive heart failure	0.867	-0.1428	0.1083
Peripheral vascular disease	0.715	-0.3355	0.0024
Cerebral vascular accident	0.831	-0.1853	0.0201
Chronic obstructive pulmonary disease	0.848	-0.1653	0.0341
Peptic ulcer disease	0.918	-0.0857	0.5592
Diabetes	0.954	-0.0471	0.6602
Acute renal failure	0.951	-0.0504	0.5492
Rheumatologic disease	0.745	-0.2948	0.1191
Mild liver disease	1.489	0.3978	0.4659
Severe liver disease	0.321	-1.1369	0.0793
Diabetes with chronic conditions	1.073	0.0708	0.623
Paraplegia	0.617	-0.4828	0.0188
Cancer diagnosis	0.972	-0.0283	0.7743
Metastasized cancer	0.555	-0.5893	0.001
HIV	<0.001	-12.044	0.965
Fecal incontinence	1.157	0.146	0.4596
Urinary incontinence	1.054	0.0529	0.5359
Depression	1.099	0.0946	0.2114
History of falls	0.657	-0.4198	0.0014
Aricept prescription	1.249	0.2225	0.005
Namenda prescription	1.132	0.1239	0.2144

Hypertension	0.943	-0.0591	0.4827
Pacemaker	0.864	-0.1466	0.3535
Defibrillator	1.402	0.3377	0.7878
Altered mental status	0.947	-0.0541	0.7892
Screen for dementia	2.057	0.7214	<.0001
Mild cognitive impairment pre-dementia	0.999	-0.0014	0.9968
Inpatient encounter count	0.672	-0.3974	0.0003
Clinic encounter	0.885	-0.1227	0.4562
Emergency room encounter	0.651	-0.43	0.0451
General medicine encounter	0.954	-0.0476	0.791
Neurology encounter	0.943	-0.0589	0.721
Psychiatry encounter	0.885	-0.1221	0.6131
SNF encounter	0.709	-0.3444	0.0865
Home health encounter	1.525	0.4218	0.369
Hospice encounter	1.489	0.3979	0.4824
Inpatient encounter count	0.985	-0.0149	0.1527
General medicine encounter count	1.032	0.0314	0.0311
Emergency room encounter count	1.022	0.0221	0.0002
Neurology encounter count	1.01	0.0101	0.1666
Psychiatry encounter count	1.007	0.00664	0.2164
SNF encounter count	0.99	-0.0101	0.4819
Home health encounter count	0.985	-0.0151	0.4555
Hospice encounter count	1.057	0.0556	0.1917

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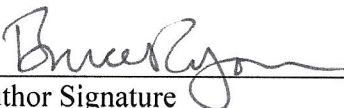variability in coronary angiography. Circulation, 53(4), 627-632.

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