Psychotropic Medication Use Among Community-Dwelling Dementia Patients: Insights from the Resources for Enhancing Alzheimer's Caregiver Health Trials

by

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To

my parents,

Lea Lewis and Loren Grace,

for their never-ending commitment to my education and well-being.

Without them, I still might not know the multiplication tables.

To

my future self,

may this serve as a reminder that with enough determination, anything is possible.

To

Cider and Sadie,

for all the walks that got cut short.

Regular trips to the park are now in order.

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Abstract

Currently, two types of medications, cholinesterase inhibitors and N-methyl d-aspartate (NMDA) receptor antagonists, are approved by the FDA for the treatment of cognitive dementia symptoms; however, there are no approved pharmacologic treatment options available for the management of mood and behavioral disturbances. As a result, several types of psychotropic medications are used "off-label" to mitigate the often troublesome, non-cognitive symptoms of dementia. This practice has come under considerable scrutiny following the 2005 and 2008 FDA black box warnings regarding the increased risk of stroke and death associated with the use of antipsychotics in elderly people with dementia.

Despite the associated risks, psychotropics are still prescribed to people with dementia. The lack of safe, alternative medications highlights the need for non-pharmaceutical interventions. In order for future interventions to be effective, they must target modifiable medication risk factors. Current research surrounding psychotropic medication use in people with dementia focuses on residents of nursing homes. Published work examining medication use among community-dwelling dementia patients is rare and none of the existing studies examine the role of informal caregivers.

The purpose of this dissertation is to investigate a broad range of care recipient and caregiver characteristics as cross-sectional and longitudinal predictors of psychotropic medication both between and within racially and ethnically diverse populations of community-dwelling dementia patients and their informal caregivers.

Using data from the Resources for Enhancing Alzheimer's Caregiver Health Trials, we found that caregiver and care recipient characteristics are important predictors of psychotropic medication use among community-dwelling dementia patients, and that the association between care recipient symptoms and medication decreases over time. Significant racial/ethnic disparities in psychotropic medication use between care recipients from three racial/ethnic groups were observed in our final study. Within race analyses revealed significant associations between Hispanic/Latino caregiver social networks and care recipient psychotropic medication use. No clear pattern was observed for other racial/ethnic groups. Future public health efforts should focus on a multidisciplinary approach to dementia care where the knowledge and skills of persons trained in cultural competence and non-pharmaceutical interventions work together with physicians and caregivers to provide a safe alternative to psychotropic medication.

Chapter 1

Introduction

Dementia is a syndrome characterized by a progressive decline in cognitive function beyond what would be expected with normal aging. It affects many areas of brain function including memory, language, problem solving and attention. Currently, dementia is an irreversible, disabling, fatal disease for which there is no cure. Although some people live well with dementia, for many patients and their families, dementia is a distressing disease. Aside from problems with memory, other common symptoms include depression, delusions, hallucinations, restlessness, wandering, agitation, aggression, and other inappropriate behaviors. Alzheimer's disease, the most common form of dementia, has a considerable personal cost and has been described as a "prolonged and tragic illness that robs the affected patient of their individuality and dignity" (1).

The impact of dementia on public health is also quite large and will continue to grow as the population ages. In 2000, there were approximately 4.5 million individuals living with Alzheimer's dementia in the United States. The prevalence is expected to reach approximately 13.2 million by the year 2050, with a disproportionate burden of disease falling on women and minorities (2, 3). A majority of dementia patients remain in the community and are cared for by relatives (4). These informal caregivers are

responsible for managing a variety of troublesome symptoms including sleep disturbances, incontinence, changes in personality, psychiatric and behavioral disturbances, and declines in self-care (5). Informal caregivers also provide a majority of the daily care that is required by an individual with dementia. The estimated value of the services provided by informal caregivers of dementia patients is approximately $18 billion annually (6).

At present, there is no cure for dementia. Treatment goals include slowing the rate of cognitive decline and mitigating mood and behavioral disturbances. There are currently two types of medications approved by the Federal Food and Drug Administration (FDA) for the treatment of cognitive dementia symptoms. These medications include cholinesterase inhibitors and N-methyl d-aspartate (NMDA) receptor antagonists. Cholinesterase inhibitors work by preventing the degradation of the neurotransmitter acetylcholine, increasing cholinergic activity in the brain (7). There are multiple cholinesterase inhibitor options available for individuals with dementia including galantamine and rivastigmine for mild and moderate dementia (8, 9), and donepezil, which is approved for use in individuals with severe dementia (10). These medications are generally well-tolerated resulting in patient compliance and patient and caregiver acceptability (11, 12). Tacrine, the first cholinesterase approved by the FDA to treat dementia, is still available; however, many patients experience severe adverse drug reactions at therapeutic doses, making newer cholinesterase inhibitors the preferred treatment option (13).

The other class of approved anti-dementia medications includes NMDA receptor antagonists. These medications block the effects of abnormal glutamate activity that lead

to neuronal cell death and cognitive dysfunction (14). Memantine, approved for moderate to severe stages of dementia, is currently the only NMDA receptor antagonist available for the treatment of dementia. It demonstrates moderate affinity binding and rapid blocking and unblocking kinetics, thus allowing enough physiologic activation of NMDA receptors required for learning and memory. Memantine is well-tolerated and is not associated with serious adverse events (15).

In addition to approved anti-dementia medications, multiple psychotropic medications including anxiolytics, antipsychotics, antidepressants, and anticonvulsants are used to treat dementia. These medications have not received a dementia indication and are used "off-label" to manage mood and behavioral symptoms. Antipsychotics have received special attention in recent years due to the 2005 and 2008 FDA-mandated black box warning concerning the increased risk of stroke and death in elderly dementia patients (16-18); however, recent work has found that these drugs are the most popular class of therapeutics among dementia patients, ranking second only to acetylcholinesterase inhibitors (19).

Other psychoactive medications used to treat mood and behavioral disturbances also have established risks. For example, benzodiazepines, a class of anxiolytic medications, are commonly used to treat anxiety and agitation in dementia despite contraindications for their use in elderly populations. It is well documented that benzodiazepines with oxidative pathways and longer half-lives are more likely to accumulate in elderly individuals, causing prolonged sedation (20). Older adults are also highly susceptible to adverse effects due to age-related increases in the brain's benzodiazepine receptors (20). As a result, elderly patients are at an increased risk of

memory loss, disinhibition, impaired psychomotor ability, and subsequently recurrent falls and hip fracture, and motor vehicle accidents (20-22). Other medications including antidepressants and anticonvulsants are associated with blurred vision and dizziness upon standing, leading to increased risk of falls and hip fracture (23, 24). These risks are even more pronounced among dementia patients where simultaneous use of multiple medications increases the likelihood of adverse drug reactions.

Despite the risks associated with psychotropic medication use in dementia patients, many physicians still advocate for their use. Pharmacologic management of difficult behaviors helps reduce the negative impact of behavioral symptoms on family caregivers and helps delay the need for institutionalization (25-27). Additionally, non-pharmacologic interventions are not reimbursable and are generally difficult to implement in practice—families caring for a demented relative often appeal for pharmacotherapy after unsuccessful attempts to manage otherwise (28-30). Unfortunately for patients, the risks associated with psychotropic medication may not be balanced by the benefit as many of these medications show only minimal to modest efficacy (31).

The practice of prescribing psychotropic medication for the management of mood and behavioral dementia symptoms has evolved out of necessity—there are currently no approved safe, pharmacologic options available. As a safeguard against many of the risks, federal guidelines regulating psychotropic medication in long-term care facilities have been established (32). Potentially modifiable risk factors for medication have also been identified in a rich body of literature examining determinants of psychotropic medication use among institutionalized elderly with dementia (33-41). Despite the

progress in our understanding of the issues surrounding psychotropic medication use among the elderly with dementia, considerable knowledge gaps remain concerning the patterns of use among demented adults living in the community. First, it is largely unknown whether caregiver attributes including perceptions of caregiving influence the risk of psychotropic medication use by the care recipient. The role of care recipient pain has also not been evaluated. Second, in spite of our knowledge regarding the increased risk of adverse events associated with psychotropic drug use in individuals with dementia, little is known about how these medications are used over time as the disease progresses and the risk of an adverse event increases. Finally, there are important health disparities in the incidence of dementia and the use of approved anti-dementia medications, with little known about the patterns of psychotropic medication use in minority, community-dwelling dementia patients.

Given the current lack of FDA approved medications for the treatment of non-cognitive dementia symptoms and serious risks associated with the use of psychotropics, the goal of research in this area should focus on gaining a more comprehensive understanding of the predictors of psychotropic medication use in order to identify potentially modifiable targets for non-pharmaceutical intervention. The studies contained within the following dissertation address this goal by utilizing a broad range of care recipient and caregiver characteristics as cross-sectional and longitudinal predictors of psychotropic medication both between and within racially and ethnically diverse populations of community-dwelling dementia patients and their informal caregivers.

1.1 Caregiver Perception of Caregiving and Care Recipient Pain as Predictors of Psychotropic Medication Use in Community-Dwelling Dementia Patients

In 2002, 58.9% of the estimated 3.4 million Medicare beneficiaries who were diagnosed with Alzheimer's disease or related dementias resided in the community (42). The use of psychotropic medication in this population is quite prevalent with estimates of the most dangerous psychotropic, antipsychotics, ranging from 14% to 27% (30, 42). Existing investigations into the predictors of psychotropic drug use in community-dwelling dementia patients have focused on patient characteristics such as age, cognitive impairment, and behavior disturbances (43-46), and have neglected the subjective caregiver experience. Informal caregivers, however, are key agents in the plan of care for patients with chronic illness such as dementia. Physicians rely on input from caregivers when assessing dementia patients and prescribing treatments (47). The lack of caregiver perceptions in the current studies of psychotropic medication use in community-dwelling dementia patients make it difficult to ascertain the extent to which subjective caregiver experience influences care recipient medication use.

Another drawback of the current literature surrounds the limited availability of data on care recipient pain. Pain perception and autonomic responses to pain are altered in dementia, and demented individuals are often unable to verbally express pain (48). As a result, it is frequently under-diagnosed and inadequately treated, resulting in pain-related behavior that can be misinterpreted as a behavioral manifestation of neurodegeneration (49). For example, it has been shown that Alzheimer's patients with arthritis are more likely to receive a benzodiazepine or neuroleptic versus an analgesic medication (50). Similar investigations have found associations between joint pain or the

presence of a painful condition and psychotropic medication use (51, 52); however, the reliance on self-reported pain measures and institutionalized dementia patients makes it difficult to glean whether community-dwelling older adults with dementia have a similar experience.

Using data from the Resources for Enhancing Alzheimer's Caregiver Health (REACH) II randomized trial, Chapter 2 examines predictors of psychotropic medication use, going beyond traditional behavioral risk factors and including caregiver perceptions of caregiving and care recipient pain in order to obtain a comprehensive understanding of the patterns of psychotropic medication use in community-dwelling elderly with dementia.

1.2 Longitudinal Predictors of Psychotropic Medication Use in Community-Dwelling Dementia Patients

The heightened concern regarding the use of psychotropic medications in the elderly is primarily due to aging-related alterations in physiology and drug metabolism which increase the risk of adverse drug reactions and toxicity. Aging individuals experience changes in the receptors that mediate drug efficacy as well as other reactions associated with side effects (53). As a result, elderly users of psychotropic medications are at an increased risk of adverse drug events. Additionally, changes in body composition that occur with age alter the distribution, metabolism, and elimination of medication, leading to an increased risk of toxicity (53). These risks are especially pronounced in the elderly with chronic conditions such as dementia, as disease pathology can exacerbate the effects of normal aging.

Understanding the predictors of psychotropic medication is an imperative first step in developing interventions aimed at minimizing their use; however, the limited number of studies investigating predictors of psychotropic medication among community-dwelling elderly with dementia in the United States were cross-sectional and have demonstrated conflicting results (43, 45, 46). Findings from cross-sectional studies with a broader focus on older adults living in the community were also inconclusive (34, 44, 54). One possible explanation for the diversity of findings may be that predictors of medication change over the course of disease, and thus vary over time. Using eighteen months of follow-up data from the REACH I randomized trial, Chapter 3 examines the longitudinal association between caregiver perceptions of caregiving, dementia patient symptoms, and the risk of care recipient psychotropic medication to determine whether the risk of medication changes over time as health declines and the risk of adverse drug events increases.

1.3 Racial and Ethnic Variation in the Use of Psychotropic Medication for the Treatment of Dementia

In the United States, racial/ethnic minorities bear a disproportionate burden of disability and disease (55). Although disparities in some health outcomes such as mortality dissipate in old age (56), multiple studies have reported a higher prevalence of dementia among minorities compared to Whites/Caucasians (2, 57, 58). Racial/ethnic differences in health care utilization, particularly the use of prescription drugs, have also been observed (59). For example, a study of Medicare beneficiaries with chronic illness found that White/Caucasian patients were more likely to use prescription medication than

Black/African Americans and Hispanic/Latinos with the same illness and insurance coverage (60).

The decreased use of prescription drugs by racial/ethnic minorities also extends to community-dwelling individuals with dementia. Several studies of non-institutionalized dementia patients have found that non-Hispanic Whites are more likely to receive FDA approved anti-dementia medication compared to minority dementia patients (61-63). In contrast, few studies of psychotropic medication use among elderly people living in the community exist and, only a small portion focuses exclusively on people with dementia. Among investigations that do focus on community-dwelling dementia patients, a comprehensive evaluation of potential racial/ethnic disparities is not possible due to either the absence of race/ethnicity data in the analysis (45, 46) or the dichotomization of race into White and non-White categories (White versus Black, White versus Other) (43, 44). Surprisingly, none of the published literature focusing on community-dwelling dementia patients examines the patterns of psychotropic medication use among community-dwelling Hispanics/Latinos with dementia. This represents an important knowledge gap as a disproportionate share of Hispanic/Latino dementia patients reside in the community and are cared for by relatives (64, 65).

Using baseline data from the REACH II randomized trial in Chapter 4, we investigated whether there were racial/ethnic disparities in the use of psychotropic medication for the treatment of dementia among a racially and geographically diverse group of community-dwelling dementia patients. We then attempted to use a broad set of caregiver and care recipient characteristics to explain the observed disparities. Finally, we examined caregiver and care recipient characteristics as predictors of psychotropic

medication within each racial/ethnic group to provide information on the patterns of use in understudied minority groups.

1.4 The Resources for Enhancing Alzheimer's Caregiver Health Trials

The analyses presented in this dissertation use data from the Resources for Enhancing Alzheimer's Caregiver Health research programs. These programs were established in 1995 by the National Institute on Aging and the National Institute on Nursing Research to develop and test interventions aimed at improving the quality of life of dementia caregivers from diverse racial/ethnic groups (66). The REACH program took place in two phases: an initial phase (REACH I) that developed and tested multiple theory-driven caregiving interventions, and a second phase (REACH II) that evaluated a single, refined, multi-component intervention. Enrollment for REACH I began in 1996 at six sites across the country including Boston, Birmingham, Memphis, Miami, Palo Alto, and Philadelphia. Participants enrolled at each site were assigned to either an active 6-month intervention or control and were followed for 18 months. Because the purpose of REACH I was to test the effectiveness of multiple intervention approaches aimed at improving various dimensions of caregiver quality of life, different interventions were implemented at each study site including: individual information and support strategy; group support and family systems therapy; psychoeducational and skill-based training approaches; home-based environmental interventions; and enhanced technology support systems (67). Consequently, REACH I yielded information about the feasibility and outcomes of multiple intervention approaches instead of providing definitive information on the efficacy of one specific strategy for enhancing caregiver quality of life (66).

Several important observations were made in REACH I. First, caregivers experienced difficulties in several areas of caregiving at varying levels of intensity. Second, active interventions were superior to control conditions in reducing caregiver burden. Finally, active interventions that emphasized caregiver engagement were the most successful at reducing caregiver depression (68). These findings identified the most promising methods for improving caregiver quality of life and helped investigators design the multi-component intervention used in REACH II.

Recruitment for REACH II began in June 2002 at five sites across the country including Birmingham, Memphis, Miami, Palo Alto, and Philadelphia. The goal of this phase of the research program was to test an intervention developed to improve caregiver depression, burden, self-care, social support, and care recipient problem behaviors. Unlike REACH I, the same intervention was used at each study site and consisted of several components including provision of information, didactic instruction, role playing, problem solving, skills training, stress management techniques, and telephone support groups (69). The intervention lasted for six months and was tailored to meet the specific needs of each caregiver. Final analyses revealed that the multi-component intervention significantly improved caregiver quality of life as measured by depression, burden, self-care, social support, and care recipient problem behaviors for White and Hispanic caregivers. Statistically significant improvements were only observed for Black, spousal care caregivers (69).

Although the goals of this dissertation include examining the predictors of psychotropic medication use in community-dwelling elderly and do not include evaluating a caregiver intervention, we chose to use the REACH data for several reasons.

First, both REACH interventions include a large number a large sample that, from a caregiver perspective, has been well-described. REACH also contains information about community-based psychotropic medication use. Finally, the REACH trials included a large number of minority caregivers and care recipients. Together, these data sets provide an ideal opportunity to test hypotheses about predictors of psychotropic medication use in community-dwelling dementia patients and to evaluate racial/ethnic disparities in psychotropic medication use.

Table 1.1 Comparison of REACH I and REACH II Interventions

	REACH I		REACH II	
Sites	Treatment	Control	Treatment	Control
Boston	Telephone-linked computer system designed with access to voicemail caregiver bulletin board, ask an expert option, and care recipient behavioral distraction	Written information about dementia caregiving and referral services	Did not participate in REACH II	
Birmingham	Skills training that stressed problem-solving	Telephone support that included empathy and active listening, and written information	Education about depression, burden, self-care, social support, and problem behaviors Teaching and practicing strategies for mood management, stress management, engaging in healthy behaviors, accessing social services, communicating with health care providers and family members, and managing care recipient problem behaviors Telephone system to connect caregivers with information	Education packet and 2 brief "check-in" calls Dementia caregiving workshop at the end of intervention
Memphis	Written information plus skills training or written information, skills training, *plus* behavior modification strategies	Written information about dementia caregiving and referral services		
Miami	In-home family systems therapy or in-home family systems therapy *plus* computer telephone integration system that provides special access to therapist	Telephone support that included empathy and active listening, and written information		

Table 1.1 Continued

	REACH I		REACH II	
Sites	Treatment	Control	Treatment	Control
Palo Alto	Coping with caregiving class that taught coping and mood management skills or enhanced support group	Telephone support that included empathy and active listening, and written information	(Copied from above) Education on depression, burden, self-care, social support, and problem behaviors Teaching and practicing strategies for mood management, stress management, engaging in healthy behaviors, accessing social services, communicating with health care providers and family members, and managing care recipient problem behaviors Telephone system to connect caregivers with information	Education packet and 2 brief "check-in" calls Dementia caregiving workshop at the end of intervention
Philadelphia	Environmental skills building program that provided caregivers with skills and technical support to modify the home	Written information about dementia caregiving and referral services		

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Chapter 2

Caregiver and Care Recipient Characteristics as Predictors of Psychotropic Medication Use in Community-Dwelling Dementia Patients

2.1 Background

The current practice of prescribing psychotropic medications to Alzheimer's and dementia patients for the management of behavior disturbances has generated substantial debate as evidence of serious side effects has emerged (1). In April 2005 the Federal Food and Drug Administration (FDA) mandated that a black box warning surrounding the increased risk of stroke and death be placed on all atypical antipsychotics. This mandate came after a meta-analysis of 17 well-designed, clinical trials among elderly dementia patients revealed that atypical antipsychotics were associated with significantly greater mortality risk versus placebo (2). The FDA warning was extended to typical antipsychotics in 2008.

Other psychotropic medications commonly prescribed to dementia patients also carry substantial risks. For example, benzodiazepines are commonly used to treat anxiety and agitation in dementia despite contraindications for their use in elderly populations due to increased risk of memory loss, increased sedation, disinhibition, impaired psychomotor ability, and subsequently recurrent falls and hip fractures (3). Tricyclic

antidepressants and selective serotonin reuptake inhibitors increase the risk of falls and hip fracture in the elderly (4).

Despite the risks associated with psychotropic medication use in dementia patients, many physicians still advocate for their use. Pharmacologic management of difficult behaviors reduces the negative impact of behavior symptoms on family caregivers and helps delay the need for institutionalization (5, 6). Additionally, non-pharmacologic interventions are not reimbursable and may be difficult for families to implement at home—families caring for a demented relative often appeal for pharmacotherapy after unsuccessful attempts to manage otherwise (7). In order to make informed decisions regarding appropriate pharmacotherapy for dementia patients, it is important to understand the determinants of psychotropic medication use.

Many investigations into the predictors of psychotropic medication use have focused on dementia patients in formal care settings and cannot be generalized to patients living in the community (8-11). One notable exception is a recent study examining determinants of atypical antipsychotic use among community-dwelling elderly currently using antipsychotic medication. Findings indicated that perceived poor mental health increased the risk of antipsychotic use (12); however, it is unknown whether these associations are influenced by the perceptions of the caregiver or exist within the subpopulation of community-dwelling, demented, elderly. Typically, within this group of patients, medication is administered by informal caregivers; however, input from caregivers is not usually considered in studies of medication use among community-dwelling dementia patients. Such information was omitted in a recent report linking

aggressive behaviors to anxiolytic and antipsychotic use in community-dwelling patients with newly diagnosed dementia (13).

The role of pain in psychotropic medication use among community-dwelling elderly with dementia is also overlooked. Pain perception and autonomic responses to pain are altered in dementia (14). Additionally, individuals with dementia are often unable to verbally express pain, and as a result, it cannot be adequately managed (15). Unaddressed pain manifests in ways that are strikingly similar to the symptoms of dementia (16). In fact, it is difficult to differentiate between behavioral and psychological symptoms of dementia and the behaviors associated with severe physical pain (1). Luijendijk *et al.* (2008) found that joint pain was associated with an increased risk of new-onset, chronic, benzodiazepine use in a cohort of non-demented persons aged 57 years or older (17). Another study found a positive association between the presence of a pain-related diagnosis and the use of psychotropic medication in elderly dementia patients (18). Both of these investigations examined people living in formal care facilities, making it difficult to determine the unique experience of dementia patients living in the community.

Given the gaps in the literature regarding the determinants of psychotropic medication use among dementia patients living outside of skilled nursing facilities, the goal of this study was to identify patient and caregiver characteristics that predict use of anxiolytics, antipsychotics, and antidepressants in the care recipient. Using data collected from the baseline assessment of the Resources for Enhancing Alzheimer's Caregiver Health II (REACH II) randomized clinical trial, we hypothesized that:

(1) Caregiving burden and patient attributes, particularly behavior disturbances and physical pain, would be associated with increases in psychotropic medication.

(2) Caregiver attributes such as vigilance, and perceived positive aspects of caregiving would be associated with decreases in psychotropic medication.

2.2 Methods

Sample

The data for this study were drawn from the baseline assessment of REACH II (ClinicalTrials.gov Identifier NCT00177489). Recruitment procedures, eligibility criteria, and psychometric properties of all measures and intervention outcomes are described elsewhere (19). The primary goal of the REACH II trial was to evaluate a multi-component, psychosocial intervention aimed at improving the quality of life of Alzheimer's caregivers. In total, 642 community-dwelling Alzheimer's care recipients and their caregivers were recruited throughout 2001-2004 from five sites across the country (Birmingham, AL; Memphis, TN; Miami, FL; Palo Alto, CA; and Philadelphia, PA). Only participants with full baseline information on study predictors and outcomes were included in the current analyses (N=598).

Outcome Measures

This study focused on care recipient use of anxiolytic, antipsychotic, and antidepressant medications as the primary outcome measures. Information on medications was collected using the "brown bag" method of medication collection (20). Accordingly, caregivers were asked to bring all currently administered medications to the

in-person interview. Medication names were recorded by study personnel and assigned a therapeutic classification code (21). Although more detailed information on drug dosages and duration of use would have been desirable, these were not collected as the analysis of prescription medication was not a primary objective of the REACH II trial.

Predictors

This study considered several caregiver characteristics and care recipient dementia symptoms as predictors of psychotropic medication use in the care recipient. Primary variables of interest included care recipient baseline cognitive status as measured by the Mini-Mental State Examination (total scores range from 0 to 30, with higher scores indicating better cognitive functioning; scores less than or equal to 24 indicate cognitive impairment) (22); care recipient functional impairment status as measured by the ability to independently perform basic and instrumental activities of daily living (ADLs and IADLs respectively; possible scores ranged from 0 to 14 with higher scores indicating more functional impairment) (23); the extent to which a caregiver was bothered by assisting with functional limitations (daily care bother; final scores ranged from 0=not at all to 4=extremely) (24); the presence of problem behaviors as measured by the Revised Memory and Behavior Problem Checklist (RMBPC) (scores range from 0-24 with higher scores indicating more problematic behaviors) (25); the extent to which caregivers were bothered by the problem behaviors (final scores ranged from 0=not at all to 4=extremely) (24); and the amount of confidence caregivers had in handling the problem behaviors (24). No direct measure of pain was collected in REACH II; however, information on care recipient analgesic medication use was available. Previous research supports the use of analgesic medication as a proxy for pain (26); therefore, care recipient

use of a narcotic or COX-2 inhibitor was utilized as a dichotomous surrogate for pain. Non-steroidal anti-inflammatory agents (NSAIDs) were not considered here as they have historically been used to manage low levels of chronic pain that cannot necessarily be eliminated (27). Additionally, NSAIDs such as aspirin are often used to decrease platelet aggregation and prevent blood clots (28). An overwhelming majority of the NSAID use in this study was aspirin (74.76%). Therefore, we focused on the presence of a narcotic or COX-2 inhibitor as surrogate for pain.

Other variables of interest focused exclusively on the caregiver and include income adequacy, as measured by perceived difficulty with paying for basics (scores range from 1=not difficult at all to 4=very difficult); self reported health (both current and current versus six months previous; scores range from 0-5 with higher scores indicating poorer health) (29); depression, as measured by the 10-item version of the Center for Epidemiological Studies-Depression Scale **(**CES-D), (scores range from 0 to 30, with higher scores indicating greater depressive symptomatology; scores of 16 or greater may indicate clinically significant depression) (30); overall caregiving burden as measured by an abbreviated, 12-item version of the Zarit Caregiver Burden Inventory (total scores range from 0 to 48, with higher scores indicating greater burden) (31, 32); caregiving mastery, assessed by eight items developed by REACH investigators (33) (total scores ranged from 0 to 16 with lower scores indicating greater mastery); vigilance, as measured by the hours per day a caregiver reported needing to be "on duty" to care for the care recipient (33); positive aspects of caregiving, as measured by the nine-item Positive Aspects of Caregiving Scale (total scores ranged from 0 to 36, with higher scores indicating more positive appraisals of the caregiving situation) (34); spiritual and

religious coping as assessed by nine questions asking caregivers to rate the extent to which religious and spiritual beliefs affect their caregiving (total scores ranged from 0 to 18 with higher scores indicating greater spiritual and religious coping) (35); and finally, dementia knowledge as measured by the caregiver's general knowledge of memory loss, dementia, and end of life legal issues (total scores range from 0 to 4, with higher scores indicating greater knowledge of dementia).

Several dimensions of social network were also examined in this investigation including network size, support satisfaction, and negative social interactions by modifying questions from several pervious measures of social interaction and support (36-38). Social network size was assessed with two questions regarding the number of people who can be counted on to provide help. Total scores range from 0 to 10 with higher scores indicating larger social networks. Caregiver satisfaction with the help received from social contacts was assessed with three questions. Total scores range from 0 to 9, with higher scores indicating more satisfaction. Finally, the presence of negative social interactions was assessed with four questions asking caregivers to rate the frequency of negative interactions on a four-point scale. Total scores ranged from 0-12 with higher scores indicating a greater frequency of negative social interactions.

Potential Confounders

This study considered care recipient race (White, Black, Hispanic, Unknown/Other), sex (male/female), age at baseline, and caregiver relationship to the care recipient (spouse/non-spouse) as potential confounders of the association between caregiver and care recipient characteristics and care recipient psychotropic medication

use. Caregiver race was highly correlated with care recipient race and was therefore not considered in this investigation.

Statistical Analysis

Descriptive statistics were computed for important demographic variables to provide a basic understanding of sample characteristics. Tetrachoric correlations between medications were also examined. Non-linear mixed models with a logit link were used to account for clustering within intervention site while estimating the association between caregiver and care recipient characteristics and care recipient psychotropic medication use. The mathematical equation for the regression models used is presented in Section 2.5, Supplemental Equations.

Based on previous observations that predictors of psychotropic medication vary across medication type (39), regression analyses for each psychotropic medication outcome proceeded in two stages. First, preliminary models were utilized to examine the association between each predictor and the odds of medication use, while controlling for confounding variables. Predictors with a p-value less than or equal to 0.10 were retained for use in the next stage of the analysis because it would be otherwise unlikely that a covariate would contribute to a multivariable model. All predictors retained from the preliminary analyses were then included in multivariable models that controlled for potential confounding variables. Estimates from the multivariable models were considered statistically significant at the 5% level.

2.3 Results

Demographic information for study participants is presented in Table 2.1. As shown in Table 2.2, care recipients displayed an average of 11 problem behaviors in the

past week. These behaviors caused caregivers "a little" to a "moderate" amount of bother. Figures 1.1 and1.2 display the prevalence of psychotropic medication use in the study sample. As shown in Figure 2.1, the prevalence of psychotropic medication use in this sample was high, with approximately 59% of participants using at least one anxiolytic, antipsychotic, or antidepressant. Figure 2.2 displays the prevalence of each psychotropic medication type. Over a quarter of care recipients were using an antipsychotic or antidepressant. Approximately 18% of care recipients used an anxiolytic. The correlation between study medications is shown in Table 2.3. Anxiolytics were significantly but weakly correlated with antipsychotics and pain medications (r=0.11 and r=0.09 respectively). Antidepressants demonstrated a significant, but weak correlation with antipsychotics (r=0.09). No significant correlations were observed between the remaining medications.

Anxiolytics

Anxiolytic medications were used by 105 care recipients. Of these care recipients, 20% were also taking an antipsychotic (n=21), 22.86% were taking an antidepressant (n=24), and 17.14% were taking all three psychotropic medications (n=18). Bivariate associations between study predictors and psychotropic medications are shown in Table 2.4. More functional impairment and increases in disruptive behaviors were significantly associated with an increased use of anxiolytics (α=0.10 for preliminary analyses). Depression, burden, and vigilance were also associated with more anxiolytic use. Larger social networks, greater confidence managing problematic behaviors, more financial strain, and greater self-reported health were associated with reduced use of anxiolytics.

Fit statistics from the multivariable model indicated that the model fit was appropriate (χ^2/df=1.03); therefore, model estimates were evaluated and are shown in Table 2.5. Less care recipient functional status, more problematic behaviors, and pain were associated with increased odds of medication use; however, the estimates were not statistically significant (OR=1.07, p=0.11; OR=1.03, p=0.37; OR=1.74, p=0.07 respectively). Caregiver vigilance was associated with greater anxiolytic use (OR=1.06, p<0.01) whereas increased confidence managing problematic behaviors was protective (OR=0.76, p=0.04).

Antipsychotics

One hundred and sixty-one care recipients were using antipsychotic medications. Of these care recipients, 14.43% had concomitant anxiolytic medication use (n=21), 32.92% had concomitant antidepressant use (n=53), and 11.18% used all three psychotropic medications (n=18) The bivariate associations presented for antipsychotic medications in Table 2.4 show that care recipient cognitive and functional impairment were associated with increased use of antipsychotics. Care recipient characteristics including poor physical health and increased hours of vigilance were also associated with increased antipsychotic use. As with anxiolytics, model fit statistics indicated that the multivariable model was an appropriate fit (χ^2/df=1.03). Results from the model are presented in Table 2.5. Compared to White care recipients, Black and Hispanic care recipients were significantly less likely to take antipsychotic medication (OR=0.60, p=0.03; OR=0.47, p<0.01 respectively). Greater care recipient functional impairment and pain was associated with increased use of antipsychotics (OR=1.08, p=0.05; OR=1.70, p=0.05). Increases in caregiver vigilance were also associated with

antipsychotic use; however, the estimate was not statistically significant (OR=1.02, p=0.28).

Antidepressants

A total of 221 care recipients were using an antidepressant medication. Of those care recipients, 10.86% were also taking an anxiolytic (n=24), 53 were also taking an antipsychotic (23.98%) and 18 were taking all three medications (8.14%). As shown in Table 2.4, higher care recipient cognitive status, greater caregiver financial strain, and more dementia knowledge were associated with greater use of antidepressants. The use of spiritual and religious coping as well as perceiving positive aspects of caregiving were associated with reduced use of antidepressants.

Model fit statistics from the multivariable model indicated that the model was an appropriate fit (χ^2/df=1.01). Results from the multivariable model are presented in Table 2.5. Younger care recipient age and better cognitive status were associated with more antidepressant use (OR=0.97, p<0.01.; OR=1.04, p<0.01 respectively). Higher levels of dementia knowledge were also associated with greater use of antidepressants (OR=1.18, p=0.02).

2.4 Discussion

This study utilized care recipient and caregiver attributes as predictors of anxiolytic, antipsychotic, and antidepressant medication use in community-dwelling dementia patients. Our findings revealed that psychotropic medication is influenced both by the needs of the care recipient and the subjective experience of the informal dementia caregiver.

In accordance with study hypotheses, more problematic behaviors were significantly associated with increased odds of anxiolytic medication, however; this association was only observed in bivariate analyses and did not remain when caregiver attributes were included in multivariable analyses. This is in contrast to Kunik *et al.* who found an increased risk of anxiolytic and antipsychotic use associated with aggressive behaviors among community-dwelling elderly with dementia (13). The lack of an observable association between problematic behaviors and psychotropic medication in this study may be partially explained by the global nature of the RMBPC. Its focus on a wide range of problematic behaviors experienced in dementia may not be sensitive enough to capture specific aggressive behaviors that would most likely be associated with psychotropic medication therapy.

Another potential explanation for the discrepant findings may be the inclusion of caregiver characteristics in the present study. Informal caregivers are key agents in the plan of care for patients with chronic illness such as dementia. Physicians rely on input from caregivers when assessing dementia patients and prescribing treatments. Failure to include caregiver assessment may exaggerate the relation between dementia symptoms and pharmacologic treatment found in the Kunik study.

We also found a positive association between pain, as measured by the use of a prescription narcotic or COX-2 inhibitor, and the use of an anxiolytic or antipsychotic medication, although the estimated effect was not statistically significant for anxiolytics. This result is consistent with a recently published study that identified joint pain as a risk factor for chronic benzodiazepine use in a cohort of non-demented, community-dwelling elderly (17) and also work that found a positive association between having a pain-related

diagnosis and the use of psychotropic medication in elderly dementia patients (18). Our results enrich these findings by generalizing the type of pain under investigation, including multiple medication outcomes, and demonstrating that the association between pain and anxiolytic use holds among demented adults living in the community.

This study is the first to comprehensively evaluate caregiver attributes as risk factors for multiple types of psychotropic medication use in community-dwelling dementia patients. In accordance with study hypotheses, we found that caregiver confidence and positive aspects of caregiving were associated with reductions in care recipient anxiolytic and antipsychotic use. This is consistent with investigations of other dementia care recipient health outcomes such as institutionalization. A 2009 review by Gaugler *et al.* found overwhelming evidence that caregiver attributes such as the feeling of losing one's self to caregiving was positively associated with institutionalization (40). There is also support for an association between a caregiver's sense of entrapment and dementia patient maltreatment (41). The consistent association between caregiver attributes and various dementia patient health outcomes suggests that an underlying causal mechanism may be acting. If so, the risk factors for psychotropic medication use identified here may also be useful for predicting other dementia patient health outcomes. Epidemiologic studies of community-dwelling dementia patients should include measures of caregiver characteristics to better elucidate the role that informal dementia caregivers play in care recipient health.

The results of this study should be considered in light of the following limitations. First, this investigation was cross-sectional and did not contain dose information and therefore cannot be used to determine the influence of caregiver and care recipient

characteristics on the intensity or duration of psychotropic medication use. Future studies with longitudinal dosing data should be utilized to examine risk factors for chronic psychotropic medication use in community-dwelling, demented populations. Second, care recipient pain was determined by the use of pain management medication. Our study found that individuals being treated with either a narcotic or COX-2 inhibitor were at an increased risk of anxiolytic or antipsychotic use. Previous research has found an association between narcotic medication use and delirium (42). Therefore, it is possible that our findings reflect a practice of polypharmacy where drug-induced delirium is addressed with psychotropic medication. Addressing this issue with cross-sectional data is difficult; however, the correlation between pain medication, anxiolytics, and antipsychotics in this study was small, suggesting that influence of polypharmacy in our study was minimal. A plausible alternative explanation of these results is that pain was not adequately managed, even among those receiving treatment. This interpretation is supported by research indicating that pain among older adults with severe cognitive impairment is often under-diagnosed and undertreated (43). Future studies should incorporate pain data either in the form of observational assessment or an inventory of painful co-morbid conditions to verify the results of this study. Third, REACH II was a randomized study. Therefore, our results are not necessarily generalizable to the population of community-dwelling dementia patients and their caregivers.

Finally, the data for REACH II were collected before the FDA issued the first black box warning on the increased risk of death associated with antipsychotics in the elderly. These warnings may be influencing current treatment patterns by shifting antipsychotic prescriptions to other pharmacologic or nonpharmacologic options. A 2010

study by Dorsey *et al.* found a substantial decrease in the use of atypical antipsychotics among elderly patients with dementia following the FDA advisory. Despite the decrease, however, atypicals remained the most popular class of therapeutics among dementia patients, ranking second only to acetylcholinesterase inhibitors in each year of the study (44). Therefore, understanding the predictors of antipsychotic drug use in community-dwelling dementia patients is still a timely and important area of gerontological research.

Despite the discussed limitations, this study establishes a benchmark for evaluating both caregiver and care recipient characteristics as risk factors for psychotropic medication use among dementia patients living in the community. This is the first study to identify caregiver confidence as a protective factor for dementia patient psychotropic medication use, and as a result, emphasizes the importance of a comprehensive approach to dementia care. Addressing the needs of informal caregivers is essential for maintaining the health and well being of the care recipient. More work is needed to assess the extent to which interventions aimed at improving caregiver confidence and appraisal reduces psychotropic medication use in dementia patients. Furthermore, our results highlight the need for better pain management strategies specifically among community-dwelling elderly with dementia.

In conclusion, this study suggests that caregiver and care recipient characteristics are important predictors of psychotropic medication use in community-dwelling dementia patients. Our work provides support for the concept of caregivers as a secondary victim of dementia by demonstrating the negative influence of long-term caregiving on caregiver mental health and subsequently the health of care recipients. Providing support services to family caregivers may be a reasonable strategy for decreasing psychotropic

drug use among community-dwelling dementia patients while also improving caregiver quality of life.

2.5 Supplemental Equations

The following equation is a mathematical representation of the non-linear mixed models used to assess study hypotheses (45).

$$logit\left(\pi_{ij}\right) = \alpha_j + \beta x_{ij} + e_{ij}$$

$$\alpha_j = \alpha + u_j$$

Where π_{ij} is the probability of medication for the ith care recipient at the jth site. α_j (j=1,…,5) is a linear combination of the grand mean (α) and a deviation (u_j), where u_j is assumed to be normally distributed $\sim N(0, \sigma_u^2)$ and independent of the care recipient level random errors (e_{ij}).

Table 2.1 Caregiver and Care Recipient Demographic Information

Demographics	Caregiver	Care recipient
Age, years		
Mean (SD)	59.55 (13.09)	79.06 (9.26)
Sex, n (%)		
Female	494 (82.61)	353 (59.03)
Male	104 (17.39)	245 (40.97)
Race, n (%)		
White	214 (35.79)	214 (35.79)
Black	192 (32.11)	186 (31.10)
Hispanic	192 (32.11)	183 (30.60)
Other/Unknown	0 (0.00)	15 (2.51)
Relationship to care recipient, n (%)		
Spouse	254 (42.47)	
Non-spouse	344 (57.53)	
Years caring for care recipient		
Mean (SD)	4.93 (7.32)	-

SD=Standard deviation

Table 2.2 Descriptive Statistics for Study Predictors and Outcomes*

Study predictors and outcomes	Mean (SD)	Range†
Care recipient attributes		
Cognitive status	12.42 (7.33)	0-30
Functional impairment	10.06 (3.11)	0-14
Number of problem behaviors endorsed	10.69 (3.98)	0-24
Pain, n (%)	75 (12.54)	-
Caregiver attributes		
Self-reported health		
Overall current health	2.11 (1.07)	0-4
Overall current health compared to 6 months previous	2.12 (0.85)	0-4
Caregiver depression	10.02 (6.51)	0-60
Caregiver burden	17.32 (8.88)	0-48
Daily care bother	0.77 (0.79)	0-4
Problem behavior bother	1.47 (0.90)	0-4
Problem behavior confidence	2.04 (0.93)	0-4
Mastery	5.94 (2.88)	0-6
Vigilance	19.30 (6.73)	0-24
Positive aspects of caregiving	25.45 (8.97)	0-36
Spiritual and religious coping	14.74 (3.54)	0-18
Social Network		
Social network size	6.38 (2.31)	0-10
Social support satisfaction	4.95 (2.82)	0-9
Negative social interaction	2.84 (2.75)	0-12
Income adequacy	1.62 (1.03)	0-3
Dementia knowledge	2.12 (1.32)	0-4
Outcomes, n (%)		
Anxiolytics	105 (17.56)	-
Antipsychotics	161 (26.92)	-
Antidepressants	221 (36.96)	-

*All values are presented as means and standard deviations, except where otherwise noted

†Range of the measurement instrument

SD=Standard deviation

Table 2.3 Correlation Between Study Medications

Variable	1	2	3	4
1. Anxiolytic	-			
2. Antipsychotic	0.11*	-		
3. Antidepressant	0.03	0.09*	-	
4. Pain (Narcotic or COX-2 inhibitor)	0.09*	0.08	0.03	-

*$p \leq 0.05$

Table 2.4 Bivariate Associations Between Study Predictors and Psychotropic Medications*

Variable	Anxiolytics		Antipsychotics		Antidepressants	
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Care recipient attributes						
Cognitive status	1.00	(0.97, 1.03)	0.97†	(0.94, 0.99)	1.04†	(1.01, 1.06)
Functional impairment	1.09†	(1.01, 1.18)	1.11†	(1.04, 1.19)	1.02	(0.97, 1.09)
Problem behavior frequency	1.06†	(1.00,1.12)	1.02	(0.97, 1.07)	1.02	(0.98, 1.06)
Pain	1.80†	(1.02, 3.19)	1.75†	(1.03, 2.97)	1.23	(0.75, 2.04)
Caregiver attributes						
Self-reported health						
Overall current health	1.26†	(1.03,1.55)	1.16†	(0.97, 1.38)	0.99	(0.85, 1.16)
Overall current health compared to 6 months previous	1.18	(0.90, 1.53)	1.30†	(1.02, 1.64)	0.96	(0.78, 1.17)
Caregiver depression	1.05†	(1.02, 1.09)	1.02	(0.99, 1.05)	1.00	(0.98, 1.03)
Caregiver burden	1.03†	(1.00, 1.05)	1.01	(0.99, 1.03)	1.01	(0.99, 1.03)
Daily care bother	0.96	(0.73, 1.27)	1.09	(0.86, 1.37)	0.99	(0.80, 1.23)
Problem behavior bother	1.20	(0.95, 1.53)	0.94	(0.76, 1.16)	1.07	(0.88, 1.29)
Problem behavior confidence	0.68†	(0.54, 0.87)	0.97	(0.80, 1.19)	1.03	(0.86, 1.24)
Mastery	1.00	(0.93, 1.08)	1.03	(0.97, 1.10)	1.01	(0.95, 1.07)
Vigilance	1.07†	(1.03, 1.12)	1.03†	(1.00, 1.06)	1.01	(0.98, 1.03)
Positive aspects of caregiving	0.99	(0.97, 1.01)	0.98	(0.96, 1.00)	0.97†	(0.96, 0.99)
Spiritual and religious coping	1.02	(0.96, 1.08)	1.02	(0.97, 1.08)	0.94†	(0.89, 0.98)
Social Network						
Social network size	0.90†	(0.82, 0.98)	1.05	(0.96, 1.14)	1.00	(0.93, 1.07)
Social support satisfaction	0.96	(0.89,1.04)	1.01	(0.95, 1.09)	0.98	(0.92, 1.04)
Negative social interaction	1.01	(0.94, 1.09)	0.98	(0.92, 1.05)	0.94	(0.89, 1.01)
Income adequacy	0.81†	(0.66, 1.00)	0.88	(0.73, 1.05)	1.16†	(0.98, 1.36)
Dementia knowledge	0.96	(0.81, 1.13)	0.95	(0.83, 1.10)	1.22†	(1.07, 1.40)

* Estimates from non-linear mixed models controlling for recipient race (White, Black, Hispanic, Unknown/Other), sex (male/female), age at baseline, and caregiver relationship to the care recipient (spouse/non-spouse)

† $p \leq 0.10$

Table 2.5 Multivariable Model Predicting Use of Anxiolytic, Antipsychotic, and Antidepressant Medication*

Variable	Anxiolytics		Antipsychotics		Antidepressants	
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Care recipient attributes						
Race						
White	REF	-	REF	-	REF	-
Black	1.72	(0.99, 3.01)	0.60†	(0.37, 0.95)	1.01	(0.66, 1.56)
Hispanic	0.94	(0.51, 1.74)	0.47†	(0.27, 0.81)	0.72	(0.46, 1.13)
Other/Unknown	2.12	(0.59, 7.62)	0.72	(0.21, 2.42)	1.05	(0.34, 3.20)
Sex						
Female	REF	-	REF	-	REF	-
Male	1.21	(0.69, 2.11)	0.64	(0.39, 1.05)	1.14	(0.73, 1.78)
Age at baseline	0.99	(0.97, 1.01)	0.99	(0.97, 1.01)	0.97†	(0.96, 0.99)
Cognitive status			0.98	(0.95, 1.00)	1.04†	(1.01, 1.06)
Functional impairment	1.07	(0.98, 1.15)	1.07†	(1.00, 1.15)		
Problem behavior frequency	1.03	(0.97, 1.09)				
Pain						
No	REF	-	REF	-	REF	-
Yes	1.74	(0.96, 3.15)	1.70†	(1.00, 2.92)		
Caregiver attributes						
Relationship to care recipient						
Spouse	REF	-	REF	-	REF	-
Non-Spouse	0.99	(0.56, 1.77)	0.94	(0.57, 1.55)	1.16	(0.74, 1.84)
Self-reported health						
Overall current health	1.08	(0.87, 1.36)	1.08	(0.89, 1.30)		
Overall current health compared to 6 months previous			1.23	(0.96, 1.57)		
Caregiver depression	1.02	(0.97, 1.06)				
Caregiver burden	1.00	(0.97, 1.03)				
Problem behavior confidence	0.76†	(0.59, 0.99)				
Vigilance	1.06 †	(1.01, 1.10)	1.02	(0.98, 1.05)		
Positive aspects of caregiving					0.99	(0.97, 1.01)
Spiritual and religious coping					0.96	(0.91, 1.01)
Social Network						
Social network size	0.94	(0.85, 1.05)				
Income adequacy	0.94	(0.74, 1.19)			1.04	(0.87, 1.24)
Dementia knowledge					1.18†	(1.02, 1.35)

*Estimates from non-linear mixed models controlling for care recipient race, sex, age at baseline, and caregiver relationship to the care recipient

†$p \leq 0.05$

Figure 2.1 Overall Prevalence of Psychotropic Medication Use

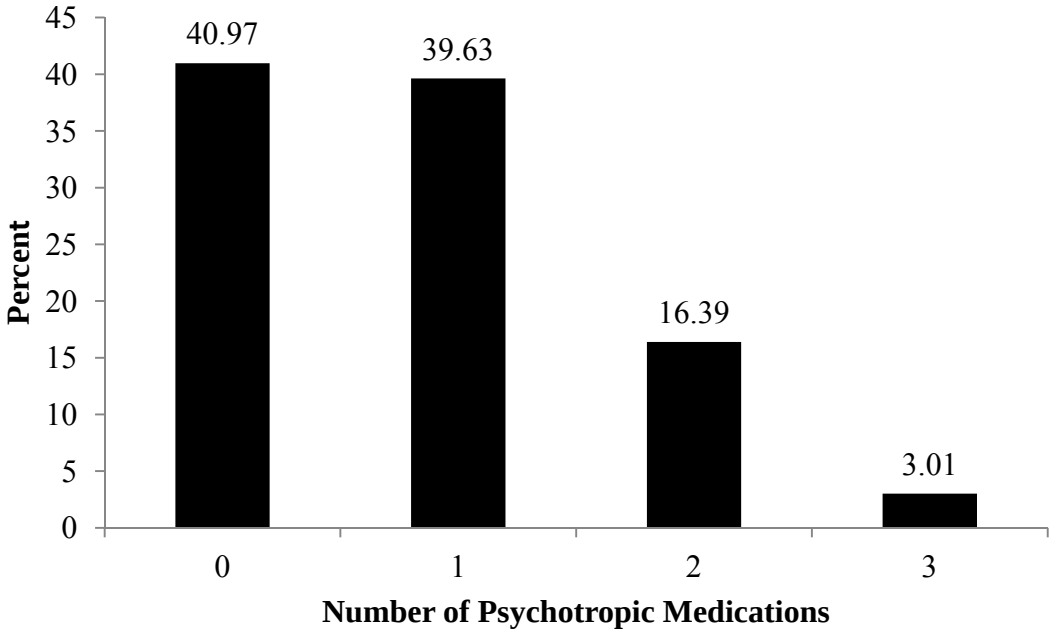
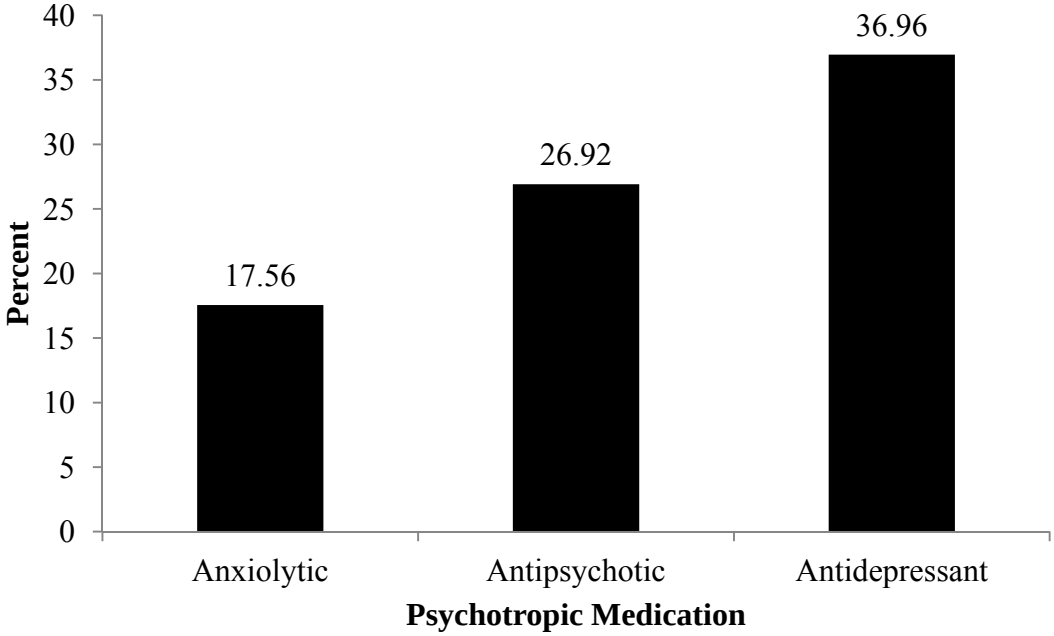


Figure 2.2 Prevalence of Psychotropic Medication Use by Medication



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Chapter 3

A Longitudinal Investigation of Psychotropic Medication Use Among Community-Dwelling Dementia Patients

3.1 Background

Psychotropic medication has a long history of use in dementia. Although never approved for this indication, several medications including anxiolytics, antipsychotics, and antidepressants were commonly used "off-label" to manage mood and behavioral symptoms of the disease (1). In April 2005, this practice came under considerable scrutiny as the Federal Food and Drug Administration (FDA) mandated that a warning surrounding the increased risk of stroke and death be placed on all atypical antipsychotics (2). The warning was extended to typical antipsychotics in 2008.

The heightened concern regarding the use of psychotropic medications in the elderly is primarily due to aging-related alterations in physiology and drug metabolism which increase the risk of adverse drug reactions and toxicity (3). Aging individuals experience changes in the receptors that mediate drug efficacy as well as other reactions associated with side effects. Additionally, changes in body composition that occur with age alter the distribution, metabolism, and elimination of these medications (3). As a result, elderly users of psychotropic medications are at an increased risk of adverse drug

reactions and drug toxicity. These risks are especially pronounced in the elderly with chronic conditions, as disease pathology can exacerbate the effects of normal aging.

Despite the risks, use of psychotropic medications is very common among elderly populations (4, 5). In the United States, research surrounding the use of psychotropic medication in the elderly is largely focused on residents of long-term care facilities (6-9). Studies of medication use among community-dwelling elderly are rare, and published work examining medication use among community-dwelling elderly with dementia are even fewer in number (4, 10-12). This is a particularly important area of research given that a majority of dementia patients remain in the community and are cared for by relatives (13).

The few studies in the US that have investigated predictors of psychotropic medication use among community-dwelling elderly with dementia have demonstrated conflicting results. An early work by Semla *et al.* found that lower cognitive function was associated with the use of antipsychotic agents and benzodiazepines. Mood changes with no precipitating cause and hallucinations were significantly associated with antipsychotic use, while depression significantly predicted use of antidepressants. Patient sex and age were not significant predictors of any study medication (12). Conversely, a more recent report did not find a significant association between disruptive behaviors and the use of any psychotropic medication, and instead found that having a greater number of co-morbid conditions and a fair/poor physical health rating independently increased the odds of antipsychotic medication use (10). Results from studies with a broader focus on community-dwelling elderly were also inconclusive (4, 11, 14, 15), suggesting that the predictors of medication may change over time and thus vary over the course of disease.

Although current work provides important insight into the predictors of psychotropic medication use among demented elderly living in the community, caregiver characteristics are consistently overlooked. This is problematic because informal caregivers are key agents in the plan of care for elderly individuals with dementia. Furthermore, most studies in this area are cross-sectional and cannot evaluate whether the association between a particular risk factor and psychotropic medication changes over time as health declines and the risk of adverse drug events increases.

Given these gaps in the literature, the goal of this study was to identify patient and caregiver characteristics that predict the use of three types of psychotropic medication (anxiolytics, antipsychotics, and antidepressants) and to determine whether the risk of psychotropic medication associated with these characteristics changes over time. Using data from the Resources for Enhancing Alzheimer's Caregiver Health (REACH) trial, we hypothesized that:

(1) Caregiving burden and dementia patient symptoms would be associated with increases in psychotropic medication, whereas resources such as social network and positive aspects of caregiving would be associated with decreases in psychotropic medication use.

(2) The association between care recipient symptoms such as problem behaviors and functional impairment, caregiver characteristics such as behavioral and impairment bother, and psychotropic medication use would be attenuated over time.

3.2 Methods

Sample

The data were drawn from the Resources for Enhancing Alzheimer's Caregiver Health I trial (ClinicalTrials.gov Identifier NCT00178165). Recruitment procedures, eligibility criteria, and psychometric properties of all measures and intervention outcomes are described elsewhere (16, 17). The primary goal of REACH I was to examine the feasibility and outcomes of multiple different intervention approaches aimed at improving Alzheimer's Caregiver quality of life. From 1996-2001, 1,222 community-dwelling Alzheimer's care recipients and their caregivers were recruited from six sites across the country (Birmingham, AL; Boston, MA; Memphis, TN; Miami, FL; Palo Alto, CA; and Philadelphia, PA) and randomized to either an active intervention or control. Single active interventions including skills training, telephone-linked computer system, and environmental skills building were used at three sites (Birmingham, Boston and Philadelphia, respectively) while the remaining sites implemented two active interventions: behavior and enhanced care (Memphis); family-based multisystem in-home intervention (FMSII) and FSMII plus a computer integrated telephone system (Miami); and coping with caregiving instruction and an enhanced support group (Palo Alto). Two sites used an information-only control condition (Boston and Philadelphia), one site provided information and referral services to the control group (Memphis), and the three remaining sites utilized an information and empathetic listening control (Birmingham, Miami, and Palo Alto). Treatment was administered for 6 months. Caregivers in both the treatment and control groups were contacted for follow-up interviews at 6, 12, and 18 months after the initial assessment (16). Only participants

with full baseline information on study variables and at least one complete follow-up assessment were included in the analyses (N=624).

Outcome Measures

This study focused on care recipient use of anxiolytic, antipsychotic, and antidepressant medications as the primary, dichotomous, outcome measures. Information on medications was collected using the "brown bag" method of medication collection (18). Accordingly, caregivers were asked to bring all currently administered medications to the in-person interview. Medication names were recorded by study personnel and assigned a therapeutic classification code (19). Although more detailed information on drug dosages and duration of use would have been desirable, these were not collected as the analysis of prescription medication was not a primary objective of the REACH trial.

Independent Variables- Design Variables

Our analysis included caregiver/care recipient dyad characteristics that were used in designing the REACH intervention study. These included categorical variables for caregiver sex and relationship to care recipient (spouse or non-spouse). Caregiver racial/ethnic identity was also a design variable; however, it is highly correlated with care recipient race, a potential confounder in this study. We therefore included care recipient racial/ethnic identity in place of caregiver racial/ethnic identity in the main analyses.

Independent Variables- Predictor Variables

This study considered several caregiver characteristics and care recipient symptoms as predictors of psychotropic medication use in the care recipient. Primary variables of interest included care recipient baseline cognitive status as measured by the Mini-Mental State Examination (total scores range from 0 to 30, with higher scores

indicating better cognitive functioning; scores less than or equal to 24 indicate cognitive impairment) (20); care recipient functional status as measured by the ability to independently perform basic and instrumental activities of daily living (ADLs and IADLs respectively; possible scores ranged from 0 to 14 with higher scores indicating more functional impairment) (21); the extent to which a caregiver was bothered by assisting with functional limitations (daily care bother; final scores ranged from 0=not at all to 4=extremely) (21); the presence of problem behaviors as measured by the Revised Memory and Behavior Problem Checklist (RMBPC) (scores range from 0-24 with higher scores indicating more problematic behaviors) (22); and the extent to which caregivers were bothered by the problem behaviors (final scores ranged from 0=not at all to 4=extremely).

Other variables of interest focused exclusively on the caregiver and include income adequacy, as measured by perceived difficulty with paying for basics (scores range from 1=not difficult at all to 4=very difficult); self-reported health (scores range from 1=poor to 5=excellent) (23); depression, as measured by the 10-item version of the Center for Epidemiological Studies-Depression Scale **(**CES-D), (scores range from 0 to 30, with higher scores indicating greater depressive symptomatology; scores of 16 or greater may indicate clinically significant depression) (24); vigilance, as measured by the hours per day a caregiver reported needing to be "on duty" to care for the care recipient (25); positive aspects of caregiving, as measured by the nine-item Positive Aspects of Caregiving Scale (total scores ranged from 0 to 36, with higher scores indicating more positive appraisals of the caregiving situation) (26); and social network size, as measured by the number of people who can be counted on to provide help (27).

Potential Confounders and Effect Modifiers

This study considered care recipient race (White, Black, Hispanic, Other), care recipient sex (male/female), and care recipient age at baseline, and intervention (treatment/control) (28) as potential confounders of the association between caregiver and care recipient characteristics and care recipient psychotropic medication use. Time was hypothesized to be an effect modifier of the association between caregiver and care recipient characteristics and medication use, and was modeled as a categorical variable with four levels representing the baseline assessment, 6 month, 12 month, and 18 month follow-up assessments.

Statistical Analysis

Before addressing study hypotheses, a preliminary analysis was undertaken to determine whether participation in a REACH I active intervention reduced care recipient psychotropic medication use. First, baseline descriptive statistics were calculated to gain a basic understanding of the distribution of demographic and medication risk factors in the treatment and control groups. Randomization was checked with Chi-Square tests for discrete data and ANOVA for continuous variables. Complete information on design variables, medication risk factors, and medication outcomes was available for 854 randomized participants. To reduce the amount of missing data, we imputed 6-month medication values for participants who had matching medication values at baseline and 12 months. Twenty-one participants received an imputed medication values making 875 participants available for analysis.

The hierarchical structure of the REACH data (i.e. participants nested within sites with different interventions and control conditions) makes multilevel regression models a

natural choice for analysis; however, this method should be used with caution when the number of clustering units is small (fewer than 5 although conservative estimates report fewer than 30) (29, 30). Multilevel models for these preliminary analyses using six clustering units did not converge, so generalized linear models with a logit link were used to determine whether participation in the active treatment group significantly reduced care recipient psychotropic medication use at the end of the 6-month intervention while controlling for site, design variables, and baseline care recipient medication use. Separate models were fit for anxiolytics, antipsychotics, and antidepressants.

To address the main study hypotheses, descriptive statistics were first computed for important baseline demographic variables. Descriptive statistics were also computed for study predictors and outcomes at each assessment to examine general trends over time. Generalized estimating equations with a logit link function and a first-order auto-regressive covariance structure were used to assess the association between caregiver and care recipient characteristics and psychotropic medication use over the study period.

Regression analyses for each outcome proceeded in multiple stages. First, main-effects models were constructed by examining the association between time, each predictor, and the odds of medication use, while controlling for site, design variables, and confounding variables. We treated intervention as a confounder in these analyses to account for its association with caregiver attributes and attrition. Predictors with a p-value less than or equal to 0.10 were retained for use in the next stage of the analysis because it would be otherwise unlikely that a covariate would contribute to a multivariable model. After the main-effects models were fit, two-way interactions between time, caregiver characteristics, and care recipient characteristics were tested and

retained if they demonstrated significance at the 5% level. In the final stage, predictors retained from the main effects model as well as significant interactions, design variables, confounders, and intervention were modeled together in a multivariable analysis. Estimates from the final, multivariable models were considered statistically significant at the 5% level. A mathematical representation of the models used in this analysis is presented in section 3.5, Supplemental Equations.

Differential loss to follow-up was examined by comparing baseline demographic and risk factor distributions between participants with and without complete follow-up information using chi-square tests for categorical characteristics and ANOVA for continuous characteristics. A sensitivity analysis was conducted by comparing results obtained from the multivariable models with all study participants to those obtained using only participants with complete follow-up information. All analyses were performed using SAS software®, v. 9.2 (Cary, NC).

3.3 Results

Results from the preliminary analysis of the REACH intervention are presented in Tables 3.1 and 3.2. Table 3.1 displays the distribution of demographic and risk factor information for the treatment and control groups. Overall, randomization was successful in balancing the intervention groups as indicated by the similarity in the distribution of most of the demographic characteristics; however one demographic factor, race, and one potential medication risk factor, daily care bother, was significantly different across intervention groups at baseline. Table 3.2 presents the results from the analysis used to assess the intervention. Active treatment was not a significant predictor of 6-month medication use for any study medication. Baseline medication use was the most

significant predictor of care recipient anxiolytic, antipsychotic, and antidepressant use at 6 months (OR=37.35, 45.48, and 51.48 respectively, $p<0.01$). A significant race effect was observed for anti-anxiety medication such that the odds of care recipient anxiolytic use during the intervention period were approximately two times higher for Hispanics compared to Whites (OR=2.26, p=0.03). Hispanics were also more likely than Whites to use antipsychotic medication although the results were not statistically significant (OR=1.94, p=0.07).

The sample used to assess the main study hypotheses included 654 REACH participants with complete baseline information and at least one complete follow-up assessment. Of these participants, 278 (42.51%) completed all follow-up assessments. Reasons for missing follow-up information included death of the care recipient (N=84, 12.84%), placement of the care recipient in a formal care facility (N=82, 12.54%), discontinuation in the study (N=85, 13.00%), and incomplete responses on study variables (N=125, 19.11%). Caregivers with complete follow-up information experienced significantly less daily care bother than caregivers without complete information. They were caring for individuals with significantly less cognitive and functional impairments, but more behavioral disruptions. Baseline demographic information is presented in Table 3.3. Caregivers in this study were, on average, 61 years old while care recipients were approximately 79 years of age. A majority of caregivers and care recipients were female. Over one-half of caregivers and care recipients were White, approximately 23% Black, and 20% Hispanic. Participants with and without complete follow-up information did not differ by age; however, there were statistically significant differences in race and caregiver sex such that participants with full

information were less likely to be Black (versus White) and more likely to have female caregivers.

Descriptive statistics for study predictors and outcomes for all participants by visit are presented in Table 3.4. At baseline, care recipients experienced a moderate amount of cognitive and functional impairment. The average total number of problematic behaviors exhibited by the care recipients in the past week was 10.11, causing caregivers "a little" to a "moderate" amount of bother. Caregivers experienced substantially less bother managing functional impairments than behavioral disturbances. The average frequency of care recipient problematic behaviors and caregiver bother decreased slightly over the study period. The prevalence of psychotropic medication use at baseline was high with half (50.46%) of participants taking at least one psychotropic medication. Approximately 18% of care recipients were using an anxiolytic or antipsychotic and nearly a third of care recipients were using an antidepressant. Antidepressants were still the most prevalent psychotropic medication at the end of the follow-up period; however, the use of anxiolytics increased to 19.00% while the percent of care recipients using an antipsychotic increased to 24.00%.

Analyses of All Study Participants

Anxiolytics

One hundred and sixteen care recipients were using an anxiolytic medication at baseline. Of these people, 9 (7.76%) were also using an antipsychotic, 38 were using an antidepressant (32.76%). Nine (7.76%) care recipients were using all three psychotropic medications. Results from the bivariate analyses of anxiolytic medication use are presented in Table 3.5. These results indicated that increases in care recipient functional

impairment and problematic behaviors were associated with slightly greater levels of care recipient medication use (OR=1.07, p=0.01 and OR=1.03, p=0.08 respectively). Caregiver characteristics including depression (OR=1.02, p=0.01), daily care bother (OR=1.28, p=0.06), and problem behavioral bother (OR=1.25, p<0.01) also exhibited a positive association with care recipient anxiolytic medication and were included in a multivariable model.

Results from the multivariable analysis of anxiolytic medication use including all 654 study participants are presented in Table 3.6. The odds of care recipient anxiolytic medication use were 2.41 times higher for Hispanics compared to Whites (OR=2.41, p<0.01). Care recipient functional status was a significant predictor of anxiolytic mediation use such that every additional functional impairment increased the odds of medication use by 6% (OR=1.06, p=0.03). Finally, a significant association between caregiver behavioral bother and care recipient anxiolytic medication use was also observed (OR=1.20, p<0.01) such that each additional unit of caregiver bother was associated with a 20% increase in medication use.

Antipsychotics

At baseline, 119 care recipients were using an antipsychotic medication. Of these people, 18.49% (n=22) had concomitant anxiolytic use while 32.77% (n=39) had concomitant antidepressant use. Nine care recipients (7.56%) were using all three psychotropic medications. Results from the preliminary analyses of antipsychotic medication use presented in Table 3.5 revealed that decreased care recipient cognitive status and more functional impairments were associated with increases in care recipient antipsychotic use (OR=0.96, p<0.01 and OR=1.07, p<0.01 respectively). Caregiver

depression exhibited a positive association with care recipient use of antipsychotic medication (OR=1.01, p=0.04).

Results from the multivariable analysis of care recipient antipsychotic medication using all 654 study participants are displayed in Table 3.6. As shown, intervention site was significantly associated with antipsychotic medication, as was relationship to the care recipient. Patients under the care of a non-spousal caregiver were 52% less likely to use an antipsychotic medication (OR=0.48, p=0.02).

Tests for the interaction between care recipient functional impairment and time indicated that the association between functional impairment and antipsychotic medication use was not constant across the study period (p=0.03). We therefore calculated the effect of functional impairment at each study follow-up and examined the relative effect of a one-unit increase in functional impairment at each visit compared to baseline. The highest odds of care recipient antipsychotic medication use associated with functional impairment was observed at baseline (OR=1.11, p<0.01); however, the odds decreased over the study time period (6 month follow-up: OR=1.06, p=0.05; 12 month follow-up: OR=1.01, p=0.75; 18 month follow-up: OR=1.01, p=0.87) (not shown due to space).

The relative effect of functional impairment at each follow-up visit compared to baseline is shown in Table 3.6. Although there is a positive association between functional impairment and care recipient medication use at each follow-up visit, the association is significantly attenuated over time. For example, the odds of medication associated with each additional functional impairment at 6-months are 5% lower than the odds observed at baseline (OR=0.95, p=0.04). Finally, a protective effect of cognitive

function was observed such that a one point increase in MMSE score reduced the odds of medication use by 3% (OR=0.97, p= 0.03).

Antidepressants

Two hundred and twelve care recipients were taking an antidepressant medication at baseline. Of those, 38 (17.93%) were also taking an anxiolytic while 39 (18.40%) were taking an antipsychotic. Nine (4.25%) care recipients were taking all three psychotropic medications. The preliminary results displayed in Table 3.5 indicated that better care recipient cognitive status was associated with increases in antidepressant use (OR= 1.02, p=0.05) while perceived positive aspects of caregiving reduced the odds of antidepressant medication (OR=0.99, p=0.10).

Results from the multivariable analysis are presented in Table 3.6. As shown, intervention site was the only significant predictor of antidepressant medication use in the multivariable model. Higher levels of care recipient cognitive function and lower levels of perceived positive aspects of caregiving increased the odds of care recipient antidepressant use, however, the estimates were not statistically significant (OR=1.03 p=0.06 ; OR=0.99, p=0.11 respectively).

Sensitivity Analyses of Participants with Full Follow-up

Anxiolytics

Table 3.7 displays results for anxiolytics from the multivariable models using only participants with complete follow-up information. Although the diminished power of this analysis resulted in non-statistically significant effects, many of the estimates obtained using only participants with complete follow-up were similar in direction and magnitude to the results obtained using all study participants with the exception of

intervention and race effects. In the analysis including only individuals with full follow-up, participation in the active treatment group reduced the odds of care recipient anxiolytic use by 3% (OR=0.97 in sensitivity analysis versus OR=1.59 in previous analysis with all study participants). The increased odds associated with being Hispanic were attenuated in the analysis containing only individuals with full follow-up versus the analysis using all eligible participants (OR=1.81 in sensitivity analysis versus OR=2.41 in previous analysis with all study participants). The odds ratios observed for functional impairment and behavioral bother in this analysis did not substantially differ from those obtained using participants with and without complete follow-up information.

Antipsychotics

Table 3.7 presents results from the multivariable models using only participants with complete follow-up information. Although limiting the sample did not change the direction of the estimates, the magnitude of the effect was influenced in one case. Care recipients under the care of a non-spousal caregiver were 80% less likely to use antipsychotic medications (OR=0.20 in sensitivity analysis versus OR=0.48 in previous analysis with all study participants). Finally, estimates for cognitive status and the interaction between functional status and time were similar to estimates obtained using all participants, although the reduced power of this analysis resulted in statistically insignificant effects.

Antidepressants

Results antidepressant analyses obtained from participants with full follow-up information presented in Table 3.7. Similar to the analysis including all participants, intervention site was one of the strongest predictors of antidepressant use. Estimates of

the association between cognitive function and medication similar in magnitude and direction (OR=0.98 in sensitivity analysis versus 0.99 in previous analysis with all study participants), as were the estimates for positive aspects of caregiving (OR=1.02 in sensitivity analysis versus 1.03 in previous analysis with all study participants).

3.4 Discussion

This study utilized longitudinal data from the REACH intervention to identify care recipient symptoms and aspects of caregiver appraisal that influence the use of anxiolytic, antipsychotic, and antidepressant medication use in community-dwelling dementia patients. Our findings revealed that the use of psychotropic medication is influenced by the mental and physical condition of the care recipient and the subjective experience of the informal dementia caregiver.

In accordance with study hypotheses, increases in caregiver behavioral bother were associated with higher odds of care recipient anxiolytic medication use; however, the frequency of problematic behaviors was not significantly associated with any study medication after inclusion in multivariable models. These findings are consistent with Chan *et al.* but are in contrast with work that has identified hallucinations (12) and aggressive behaviors (11) as predictors of psychotropic drug use in community-dwelling dementia patients. The lack of an observable association between problematic behaviors and psychotropic drug use in this study may be partially explained by the global nature of the behavior measurement instrument used in this study. The RMBPC includes a wide range of problematic behaviors experienced in dementia and may not be sensitive enough to capture specific aggressive behaviors that would most likely be associated with psychotropic medication.

Another potential explanation may be the inclusion of caregiver characteristics in the current study. Physicians rely on input from caregivers when assessing dementia patients and prescribing treatments. Failure to include caregiver assessment may exaggerate the relation between dementia symptoms and psychotropic medication use found in other studies. This explanation is supported by our data as problematic behaviors demonstrated a significant, positive association with anxiolytic use in preliminary analyses, but not in multivariable models that included caregiver burden.

We also observed a positive association between care recipient functional impairment and the use of anxiolytic and antipsychotic medications, although the association observed for antipsychotics was significantly attenuated over the study period. While functional impairment was not considered in several investigations of psychotropic medication use in community-dwelling elderly with dementia (12, 15, 31, 32), our finding of a positive association between impairment and medication is consistent with work presented by Gustafsson *et al*. and Aparasu *et al.* (4, 33). No significant association between functional impairment and psychotropic medication was reported by Chan *et al*. (10). These discrepant findings may be explained, in part, by the variable relation between functional impairment and use of antipsychotic medication. Our findings suggest that antipsychotic medications are most widely used during the early and moderate stages of physical decline but are used more judiciously over time as the risk of adverse drug reactions increases. This pattern corresponds with guidelines established for other dementia medications such as cholinesterase inhibitors (34, 35). Consequently, cross-sectional studies of severely impaired community-dwelling dementia

patients may fail to find an association between functional impairment and antipsychotic use.

Although not a main focus of this study, we evaluated whether the 6-month REACH intervention influenced care recipient psychotropic medication use. Results indicated that the psychosocial interventions offered in REACH did not influence the use of any study medications; however, both the intervention and repeated measure analyses revealed potential racial and ethnic disparities in the pharmacologic management of dementia. Although the role of culture and race/ethnicity has been largely ignored in the literature on psychotropic drug use in community dwelling dementia patients, our preliminary findings are commensurate with recently published work that found racial and ethnic disparities in the utilization of medications approved to treat cognitive symptoms of dementia (36). Future work with a focus on recruiting minority dementia patients and caregivers is needed to understand whether racial/ethnic disparities in the treatment of dementia with psychotropic medication exist and whether care recipient symptoms and caregiver characteristics differentially influence psychotropic medication use across various racial/ethnic groups.

The results of this study should be considered in light of the following limitations. First, the sample used for this study consisted of care recipients who were at the moderate to severe stage of dementia and had already experienced a substantial amount of cognitive and functional decline. As a result, we were not able to capture the nature of the relation between functional impairment and care recipient psychotropic medication use across all stages of dementia. Although analyses revealed that the effect of functional impairment on antipsychotic medication was attenuated over time, the odds ratio

associated with functional impairment was not significantly different from one at the 12 or 18 month visit. It is plausible that a more pronounced association between functional impairment and antipsychotic use would have been observed had participants been enrolled in earlier stages of disease. Future studies utilizing longer follow-up periods and participants at various stages of dementia are needed to accurately characterize the role of functional impairment in care recipient psychotropic medication use.

Second, one must consider the possibility that the observed results are due to attrition bias. Caregivers who remained in the study experienced significantly less daily care bother than caregivers who discontinued. Therefore, it is possible that, in the presence of a true positive association between daily care bother and care recipient psychotropic medication use, the findings presented here are biased towards the null. Inferences regarding care recipient characteristics are also vulnerable to attrition bias. Care recipients completing all follow-up visits experienced significantly less cognitive and functional impairment than those without complete follow-up. It is therefore possible that the observations concerning cognitive and functional impairment are also biased towards the null. For example, the attenuated effect of functional impairment on antipsychotic medication use over time may have been more pronounced had care recipients with more severe functional impairment remained in the study. A sensitivity analysis conducted only on individuals with complete follow-up suggests that the influence of attrition bias on the direction of study results is small.

Finally, information on medication dosages was not available in the REACH trial. Consequently, we are unable to comment on the extent to which care recipient and caregiver characteristics influence the intensity of psychotropic drug use in community-

dwelling dementia patients. It is conceivable that using a more sensitive measure of medication would identify associations that were not detected here. Future work should include information on drug dosages in order to obtain a comprehensive picture of psychotropic medication use in community-dwelling dementia patients.

Despite the discussed limitations, this study provides valuable information regarding psychotropic drug use patterns among community-dwelling dementia patients in the United States. To our knowledge, this is the first investigation to identify a variable association between functional impairment and antipsychotic medication use across time, suggesting that, despite the lack of formal guidelines that exist for FDA approved medications, physicians may be less likely to suggest pharmacologic treatment strategies as physical health declines.

This study also identified caregiver behavioral bother as a risk factor for dementia patient anxiolytic medication use and as a result, emphasizes a comprehensive approach to dementia care. Addressing the burden associated with managing problematic behaviors may be an effective way of reducing psychotropic medication use among elderly dementia patients residing in the community. More work is needed to identify caregiver interventions that can successfully reduce care recipient medication use.

In conclusion, this study suggests that caregiver and care recipient characteristics are important predictors of psychotropic medication use in community-dwelling dementia patients, and that the risk of antipsychotic medication associated with care recipient functional impairment declines over time. Reducing caregiver behavioral bother through the use of non-pharmacological interventions may be a reasonable strategy for decreasing

anxiolytic drug use among community-dwelling dementia patients while also improving caregiver quality of life.

3.5 Supplemental Equations

The following equation is a mathematical representation of the generalized estimating equation used to assess study hypotheses (37).

$$logit\left(\pi_{ij}\right) = \alpha + \beta x_{ij} + e_{ij}$$

Where π_{ij} is the probability of medication for the ith care recipient at the jth time point (j=0,1,2,3). The errors, e_{ij} are assumed to have a multivariate normal distribution with mean 0 and variance Σ, where

$$\Sigma = \sigma^2 \begin{bmatrix} 1 & \rho & \rho^2 & \rho^3 \\ & 1 & \rho & \rho^2 \\ & & 1 & \rho \\ & & & 1 \end{bmatrix}$$

Table 3.1 Baseline Demographic and Risk Factor Information for Intervention Analysis*

	Treatment (N=558)	Control (N=317)
Caregiver variables		
Race† (n,%)		
White	301 (53.94)	180 (56.78)
Black	119 (21.33)	99 (31.23)
Hispanic	135 (24.19)	37 (11.67)
Other	3 (0.54)	1 (0.32)
Sex		
Female	464(83.15)	250 (78.86)
Male	94 (16.85)	67 (21.14)
Age	61.31 (13.81)	62.25 (12.81)
Relationship to the care recipient (n,%)		
Spouse	266 (47.67)	145 (45.74)
Non-spouse	292 (52.33)	172 (54.26)
Years providing care	4.30 (4.22)	4.50 (4.71)
Income adequacy	2.20 (1.06)	2.25 (1.07)
Depression	22.68 (8.42)	22.07 (7.83)
Daily care bother†	0.30 (0.55)	0.38 (0.61)
Behavioral bother	1.46 (0.91)	1.40 (0.88)
Social network	16.89 (4.70)	13.99 (4.99)
Care recipient Variables		
Race† (n,%)		
White	299 (53.58)	178 (56.15)
Black	121 (21.68)	98 (30.91)
Hispanic	127 (22.76)	37 (11.67)
Other	11 (1.97)	4 (1.26)
Sex		
Female	318 (56.99)	181 (57.10)
Male	240 (43.01)	136 (42.90)
Age	78.81 (11.03)	79.63 (7.80)
Cognitive status	12.92 (7.65)	12.45 (7.72)
Functional status	10.44 (2.77)	10.68 (2.91)
Number of problem behaviors	10.36 (4.16)	9.83 (4.04)

*Information presented as mean (standard deviation) unless otherwise specified

† $p \leq 0.05$

Table 3.2 Results from the REACH Intervention Analysis[*]

	Anxiolytics		Antipsychotics		Antidepressants	
	Odds Ratio	95% Confidence interval	Odds Ratio	95% Confidence interval	Odds Ratio	95% Confidence interval
Site						
Philadelphia	REF	-	REF	-	REF	-
Birmingham	0.65	(0.26, 1.61)	0.98	(0.44, 2.18)	1.46	(0.66, 3.23)
Boston	0.94	(0.29, 3.02)	2.17	(0.83, 5.66)	0.79	(0.29, 2.17)
Memphis	0.96	(0.46, 1.96)	0.57	(0.27, 1.17)	1.08	(0.54, 2.15)
Miami	1.03	(0.26, 2.07)	1.36	(0.53, 3.51)	1.49	(0.61, 3.66)
Palo Alto	0.67	(0.20, 1.73)	0.72	(0.28, 1.81)	0.61	(0.26 1.47)
Intervention						
Control	REF	-	REF	-	REF	-
Treatment	0.93	(0.55, 1.55)	0.84	(0.52, 1.35)	0.87	(0.54, 1.40)
Caregiver race						
White	REF	-	REF	-	REF	-
Black	0.69	(0.31, 1.10)	1.41	(0.77, 2.61)	0.58	(0.31, 1.08)
Hispanic	2.01	(1.03, 4.18)[†]	1.94	(0.95, 3.93)	0.76	(0.38, 1.51)
Other	1.06	(1.05, 22.87)	0.79	(0.02, 30.39)	0.76	(0.02, 27.03)
Caregiver sex						
Female	REF	-	REF	-	REF	-
Male	0.67	(0.36, 1.27)	1.08	(0.59, 1.95)	1.00	(0.56, 1.81)
Relationship to care recipient						
Spouse	REF	-	REF	-	REF	-
Non-spouse	1.06	(0.64, 1.77)	0.98	(0.56, 1.48)	0.63	(0.39, 1.02)
Daily care bother	1.39	(0.89, 2.18)	1.43	(0.92, 2.24)	1.14	(0.74, 1.77)
Baseline medication[§] use	37.35	(23.14, 60.27)[†]	45.48	(27.97, 72.94)[†]	51.48	(34.92, 85.00)[†]

[*]Estimates from generalized linear models controlling for study design variables including site, caregiver sex, caregiver race, relationship to the care recipient; also controlled for daily care bother, and baseline medication use

[†]$p \leq 0.05$

[§]Medication refers to the specific medication used in the model

Table 3.3 Baseline Demographic Information for Analyses of Main Study Hypotheses

Demographic Variables	All (N=654)	Full Information (N=278)	Incomplete Information (N=376)
Age at baseline, Mean (SD)			
Caregiver	60.99 (13.48)	60.52 (13.63)	61.33 (13.37)
Care recipient	79.31 (9.49)	78.35 (11.06)	80.03 (8.07)
Race, n (%)			
Caregiver*			
White	361 (55.20)	159 (57.19)	202 (53.72)
Black	150 (22.94)	42 (15.11)	108 (28.72)
Hispanic	140 (21.41)	76 (27.34)	64 (17.02)
Other	3 (0.46)	1 (0.36)	2 (0.53)
Care recipient*			
White	361 (55.20)	160 (57.55)	201 (53.46)
Black	152 (23.24)	45 (16.19)	107 (28.46)
Hispanic	132 (20.18)	69 (24.82)	63 (16.76)
Other	9 (1.38)	4 (1.44)	5 (1.32)
Sex, n (%)			
Caregiver*			
Male	111 (16.97)	37 (13.31)	74 (19.68)
Female	543 (83.03)	241 (86.69)	302 (80.32)
Care recipient			
Male	273 (41.74)	126 (45.32)	147 (39.10)
Female	381 (58.26)	152 (54.68)	229 (60.90)
Relationship to the care recipient, n (%)			
Spouse	289 (44.19)	132 (47.48)	157 (41.76)
Non-Spouse	365 (55.81)	146 (52.52)	219 (58.24)
Years providing care, Mean (SD)	4.45 (4.57)	4.37 (4.82)	4.50 (4.38)

*$p \leq 0.05$ for chi-square test of homogeneity

Table 3.4 Descriptive Statistics for Study Predictors and Outcomes by Visit for All Participants*

Study predictors and outcomes	Range†	Baseline (n=654)	6 month follow-up (n=628)	12 month follow-up (n=363)	18 month follow-up (n=300)
Care recipient symptoms					
Cognitive status	0-30	13.35 (7.59)	X	X	X
Functional status	0-14	10.41 (2.87)	10.96 (2.81)	11.03 (2.81)	11.25 (2.76)
Number of problem behaviors Endorsed	0-24	10.11 (4.06)	9.47 (4.14)	9.56 (4.06)	9.71 (4.33)
Caregiver attributes					
Income adequacy	0-3	2.21 (1.06)	2.16 (1.05)	2.09 (1.05)	2.16 (1.08)
Overall current health	1-5	2.98 (1.05)	2.92 (1.04)	3.00 (1.06)	2.93 (1.06)
Caregiver depression	0-30	14.95 (11.01)	14.28(10.61)	13.87 (10.89)	13.21 (9.97)
Daily care bother	0-4	0.28 (0.53)	0.30 (0.58)	0.20 (0.47)	0.20 (0.51)
Problem behavioral bother	0-4	1.43 (0.89)	1.35 (0.90)	1.29 (0.88)	1.26 (0.84)
Vigilance	0-24	18.27 (7.73)	18.50 (7.59)	18.23 (7.75)	18.44 (7.64)
Positive aspects of caregiving	0-36	34.35 (8.81)	34.66 (9.07)	34.94 (8.96)	35.44 (8.00)
Social network	0-30	16.69 (5.52)	16.59 (5.54)	16.87 (5.14)	16.96 (5.44)
Outcomes, n (%)					
Anxiolytics	-	116 (17.74)	115 (18.31)	64 (17.63)	57 (19.00)
Antipsychotics	-	119 (18.20)	122 (19.56)	84 (23.14)	72 (24.00)
Antidepressants	-	212 (32.42)	197 (31.37)	120 (33.06)	96 (32.00)

*All values are presented as means and standard deviations, except where otherwise noted
†Range of the measurement instrument
SD=standard deviation

Table 3.5 Results From Preliminary Analyses Examining the Association Between Each Predictor, and the Odds of Medication Use[*]

Variable	Anxiolytics		Antipsychotics		Antidepressants	
	Odds Ratio	95% Confidence interval	Odds Ratio	95% Confidence interval	Odds Ratio	95% Confidence interval
Care recipient symptoms						
Cognitive status	0.99	(0.97, 1.01)	0.96	(0.94, 0.99)[†]	1.02	(1.00, 1.04) [†]
Functional status	1.07	(1.02, 1.13)[†]	1.07	(1.02, 1.12)[†]	0.99	(0.97, 1.03)
Number of problem behaviors	1.03	(1.00, 1.06)[†]	1.01	(0.99, 1.04)	1.00	(0.98, 1.03)
Caregiver attributes						
Income Adequacy	1.03	(0.92, 1.16)	1.03	(0.92, 1.14)	1.03	(0.94, 1.12)
Overall current health	0.58	(0.84, 1.07)	1.00	(0.90, 1.10)	0.97	(0.89, 1.05)
Caregiver depression	1.02	(1.00, 1.03)[†]	1.01	(1.00, 1.02)[†]	1.00	(1.00, 1.01)
Daily care bother	1.28	(0.99, 1.66)[†]	1.15	(0.91, 1.45)	1.16	(0.94, 1.43)
Problem behavioral bother	1.25	(1.11, 1.40)[†]	1.06	(0.95, 1.19)	1.03	(0.94, 1.13)
Vigilance	1.00	(0.99, 1.01)	1.00	(0.99, 1.01)	1.00	(0.99, 1.01)
Positive aspects of caregiving	0.99	(0.98, 1.00)	0.99	(0.97, 1.00)	0.99	(0.98, 1.00) [†]
Social network	0.99	(0.97, 1.01)	0.99	(0.97, 1.01)	1.00	(0.98, 1.02)

[*] Estimates from generalized linear models controlling for site, intervention assignment, caregiver relationship to the care recipient, caregiver sex, care recipient sex, care recipient race, and care recipient age at baseline

[†] $p \leq 0.10$

Table 3.6 Results From Multivariable Analyses Including All Study Participants*

	Anxiolytics		Antipsychotics		Antidepressants	
Variable	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
Intervention						
Control	REF	-	REF	-	REF	-
Treatment	1.59	(1.07 2.37)†	0.88	(0.60, 1.28)	0.91	(0.66, 1.27)
Site						
Philadelphia	REF	-	REF	-	REF	-
Birmingham	1.52	(0.71, 3.26)	2.93	(1.56, 5.53)†	1.47	(0.78, 2.81)
Boston	0.50	(0.20, 1.50)	1.58	(0.62, 4.04)	1.03	(0.51, 2.08)
Memphis	1.18	(0.64, 2.17)	1.59	(0.90, 2.81)	1.66	(1.00, 2.76)†
Miami	1.32	(0.67, 2.56)	1.67	(0.88, 3.18)	2.01	(1.14, 3.53)†
Palo Alto	0.642	(0.34, 1.23)	0.90	(0.49, 1.68)	0.91	(0.54,1.51)
Relationship to care recipient						
Spouse	REF	-	REF	-	REF	-
Non-spouse	1.15	(0.64, 2.10)	0.48	(0.25, 0.91)†	0.96	(0.58, 1.60)
Caregiver sex						
Female	REF	-	REF	-	REF	-
Male	1.02	(0.56, 1.88)	0.61	(0.31, 1.21)	0.82	(0.48, 1.39)
Care recipient sex						
Female	REF	-	REF	-	REF	-
Male	1.24	(0.69, 2.27)	0.75	(0.41, 1.39)	0.77	(0.47, 1.28)
Care recipient race						
White	REF	-	REF	-	REF	-
Black	0.71	(0.43, 1.22)	1.20	(0.74, 1.96)	0.68	(0.44, 1.06)
Hispanic	2.41	(1.49, 3.91)†	1.41	(0.86, 2.31)	0.65	(0.40, 1.04)
Other	0.41	(0.05, 3.50)	1.82	(0.41, 8.12)	0.52	(0.14, 1.87)
Baseline age	1.01	(0.99, 1.03)	1.00	(0.98, 1.02)	0.98	(0.96, 1.00)

Table 3.6 continued

Variable	Anxiolytics		Antipsychotics		Antidepressants	
	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
Visit						
Baseline	REF	-	REF	-	REF	-
6-month	1.01	(0.83, 1.22)	-	-	0.98	(0.86, 1.11)
12-month	0.97	(0.78, 1.21)	-	-	1.02	(0.87, 1.20)
18-month	1.18	(0.93, 1.50)	-	-	0.95	(0.81, 1.13)
Cognitive status	-	-	0.97	(0.95, 0.99)†	1.02	(1.00, 1.04)
Functional status	1.06	(1.01, 1.12)†	-	-	-	-
Functional status*visit						
Functional status						
Baseline	-	-	REF	-	-	-
6-month	-	-	0.95	(0.90, 1.00)†	-	-
12-month	-	-	0.90	(0.85, 0.97)†	-	-
18-month	-	-	0.90	(0.83, 0.98) †	-	-
Daily care bother	1.14	(0.88, 1.47)	-	-	-	-
Problem behavior frequency	1.00	(0.97, 1.03)	-	-	-	-
Problem behavioral bother	1.20	(1.05, 1.36)†	-	-	-	-
Caregiver depression	1.01	(1.00, 1.02)	1.01	(1.00, 1.02)	-	-
Positive aspects of caregiving	-	-	-	-	0.99	(0.98, 1.00)

* Estimates from generalized linear models controlling for site, intervention assignment, caregiver relationship to the care recipient, caregiver sex, care recipient sex, care recipient race, and care recipient age at baseline

† $p \leq 0.05$

Table 3.7 Results From Multivariable Analyses for Participants With Full Follow-Up Information*

	Anxiolytics		Antipsychotics		Antidepressants	
Variable	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
Intervention						
Control	REF	-	REF	-	REF	-
Treatment	0.97	(0.48, 1.99)	0.42	(0.23, 0.78)	0.98	(0.56, 1.71)
Site						
Philadelphia	REF	-	-	-	-	-
Birmingham	1.84	(0.43, 7.82)	1.27	(0.41, 3.97)	1.97	(0.67, 5.81)
Boston	0.21	(0.02, 1.95)	1.23	(0.32, 4.70)	0.99	(0.31, 3.16)
Memphis	1.29	(0.34, 4.86)	1.45	(0.51, 4.09)	1.66	(0.62, 4.39)
Miami	1.57	(0.39, 6.28)	1.35	(0.47, 3.87)	2.38	(0.83, 6.82)
Palo Alto	1.22	(0.32, 4.65)	0.86	(0.31, 2.40)	0.84	(0.32, 2.18)
Relationship to care recipient						
Spouse	REF	-	REF	-	REF	-
Non-spouse	0.73	(0.22, 2.35)	0.20	(0.06, 0.67)	1.46	(0.58, 3.69)
Caregiver sex						
Female	REF	-	REF	-	REF	-
Male	0.80	(0.25, 2.58)	0.44	(0.13, 1.48)	0.64	(0.23, 1.75)
Care recipient sex						
Female	REF	-	REF	-	REF	-
Male	0.77	(0.25, 2.36)	0.33	(0.10, 1.02)	0.75	(0.31, 1.85)
Care recipient race						
White	REF	-	REF	-	REF	-
Black	0.43	(0.14, 1.34)	1.78	(0.82, 3.88)	0.47	(0.22, 1.02)
Hispanic	1.81	(0.90, 3.62)	1.57	(0.76, 3.22)	0.54	(0.28, 1.06)
Other	0.82	(0.11, 6.11)	5.64	(0.88, 36.18)	0.14	(0.03, 0.72)
Baseline age	1.02	(0.99, 1.05)	1.00	(0.98, 1.03)	0.98	(0.95, 1.01)

Table 3.7 continued

Variable	Anxiolytics		Antipsychotics		Antidepressants	
	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
Visit						
Baseline	REF	-	-	-	-	-
6-month	0.91	(0.67, 1.22)	-	-	0.95	(0.80, 1.15)
12-month	1.05	(0.77, 1.43)	-	-	1.04	(0.85, 1.29)
18-month	1.26	(0.90, 1.73)	-	-	0.95	(0.76, 1.19)
Cognitive status	-	-	0.99	(0.88, 1.07)	1.02	(0.99, 1.05)
Functional status	1.01	(0.94, 1.10)	-	-	1.02	(0.99, 1.05)
Functional status*visit						
Functional status						
Baseline	-	-	REF	-	-	-
6-month	-	-	0.98	(0.93, 1.05)	-	-
12-month	-	-	0.97	(0.89, 1.05)	-	-
18-month	-	-	0.97	(0.96, 1.13)	-	
Daily care bother	1.10	(0.94, 1.29)	-	-	-	-
Problem behavior frequency	1.01	(0.96, 1.05)	-	-	-	-
Problem behavioral bother	1.10	(0.94, 1.29)	-	-	-	-
Caregiver depression	1.00	(0.98, 1.02)	1.00	(0.99, 1.02)	-	-
Positive aspects of caregiving	-	-	-	-	0.98	(0.97, 0.99)

* Estimates from generalized linear models controlling for site, intervention assignment, caregiver relationship to the care recipient, caregiver sex, care recipient sex, care recipient race, and care recipient age at baseline† $p \leq 0.05$

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Chapter 4

Racial and Ethnic Disparities in Psychotropic Medication Use Among Community-Dwelling Dementia Patients

4.1 Background

There are currently two classes of medications approved by the FDA for the treatment of Alzheimer's disease and related disorders: cholinesterase inhibitors for the early to moderate stages of dementia, and NMDA receptor antagonists for moderate to severe disease stages. These medications are primarily used to delay the progression of cognitive symptoms (1). Previous investigations of approved anti-dementia medications have uncovered racial/ethnic differences in drug utilization with non-Hispanic White patients receiving more prescriptions for anti-dementia treatments relative to minority patients (2-5). This difference is particularly concerning considering that older African Americans and Latinos are part of the fastest growing sector of the US elderly population and are more likely than older Caucasians to have Alzheimer's disease and other dementias (6, 7).

A wide variety of psychotropic medications including anxiolytics, antipsychotics, and antidepressants are also used in the treatment of dementia. Although not approved by the FDA, these medications are often prescribed off-label to manage mood and behavioral symptoms (8). Compared to FDA approved dementia medications, relatively

little is known about the patterns of psychotropic medication in minority dementia patients and whether racial/ethnic disparities exist. A majority of the existing work in this area focuses on relatively homogeneous nursing home populations and cannot be generalized to people residing in the community (9-15). Few studies of psychotropic medication use among elderly people living in the community exist (16-20), and only a small portion focus exclusively on elderly with dementia. Among investigations that do examine the use of psychotropic medications by community-dwelling dementia patients, a comprehensive evaluation of potential racial/ethnic differences is not possible due to either the absence of race/ethnicity data in the analysis (21, 22) or the dichotomization of race into White and non-White categories (White versus Black, White versus Other) (23). None of the published literature focusing on community-dwelling dementia patients has examined the patterns of psychotropic medication use specifically within community-dwelling Hispanics/Latinos with dementia. This omission represents a considerable knowledge gap as a disproportionate share of Hispanic/Latino dementia patients reside in the community and are cared for by relatives (24, 25).

Typically, differential access and utilization of health care and differences in health outcomes by a demographic group is considered a health disparity. Within the areas of public health and social sciences, the term "disparity" may also carry with it a connotation of injustice based on the view that health inequalities are unnecessary and avoidable (26) . Disparities can exist across several demographic groups including age, sex, and race/ethnicity. In many situations, the consequence of a disparity is clear. For example, influenza vaccination rates are substantially lower in elderly Black/African Americans and Hispanic/Latinos compared to elderly White/Caucasians (27). This

disparity represents a clear disadvantage for minority elders as influenza vaccines are highly effective at reducing morbidity and mortality associated with influenza (27).

Consequences of disparities in psychotropic medication use among community-dwelling dementia patients are not as straightforward. Although psychotropic medications demonstrate some efficacy in reducing mood and behavioral disturbances in dementia, they are also associated with substantial risks (28-30). It is therefore unclear whether racial/ethnic differences in psychotropic medication use necessarily represent a disadvantage for the demographic groups receiving the least medication. Consequently, we will refer to differences in the use of psychotropic medication across race as racial/ethnic disparities in medication use without implying a direction of disadvantage.

Multiple conceptual models are available to help understand the determinants of psychotropic medication use in dementia caregiving and also to understand how racial/ethnic disparities in medication use arise (31-33). These models highlight the multifactorial nature in which race/ethnicity can influence caregiving outcomes including differential exposure to hazards or stressors that influence health and exacerbate disease; unequal access to financial and educational resources that buffer the effects of stressors; and variability in cultural norms that influence perceptions of caregiving, coping strategies, and social support availability. Although conceptual models provide a useful framework for thinking about how race/ethnicity influences health outcomes, it is often difficult to find data sources that are able to address all model components. A majority of the existing work on racial/ethnic differences in anti-dementia medication among community-dwelling elderly people relies on billing data (34) or cohorts of elderly people that focus solely on the care recipient, thereby lacking information on informal caregivers

(2, 3, 5). Informal caregivers are key agents for the plan of care for elderly individuals with dementia, and caregivers from different racial/ethnic groups may vary in the perceived intensity of stressors and coping strategies that are relevant to health outcomes (35). For example, the use of spiritual religious coping mechanisms by African American caregivers combined with cultural perceptions of caregiving likely influence the decision of whether or not to initiate psychotropic medication (36). The extent to which caregiver characteristics influence care recipient psychotropic medication in minority populations and whether caregiver characteristics account for differences in medication use across diverse populations is unknown.

Given the gaps in the literature surrounding the use of psychotropic medication in diverse groups of community-dwelling dementia patients, we first focused on documenting racial/ethnic disparities in the use of three psychotropic medications (anxiolytics, antipsychotics, and antidepressants). We then identified variables that explained racial/ethnic disparities in psychotropic medication as potential targets for future interventions. Using data from the Resources for Enhancing Alzheimer's Caregiver Health (REACH) II randomized trial, we hypothesized that

(1) The prevalence of psychotropic medication would be higher in non-Hispanic Whites compared to Hispanics/Latinos or Black/African Americans, and

(2) Observed differences between racial/ethnic groups would be explained by, caregiver socioeconomic factors, care recipient characteristics, caregiver health, perceptions of caregiving, or non-financial resources.

Given the lack of data regarding the predictors of psychotropic medication within minority, community-dwelling, dementia patients, another goal was to examine predictors of care recipient psychotropic medication within racial/ethnic groups. This information will give clinicians a better understanding of the needs of the patients and caregivers they serve, and may also help inform future interventions aimed at decreasing off-label use of psychotropic medications.

4.2 Methods

Sample

The data for this study were drawn from the baseline assessment of REACH II (ClinicalTrials.gov Identifier NCT00177489). Recruitment procedures, eligibility criteria, and psychometric properties of all measures and intervention outcomes are described elsewhere (37). The primary goal of the REACH II trial was to evaluate a multi-component, psychosocial intervention aimed at improving the quality of life of Alzheimer's caregivers. In total, 642 community-dwelling Alzheimer's care recipients and their caregivers were recruited throughout 2001-2004 from five sites across the country (Birmingham, AL; Memphis, TN; Miami, FL; Palo Alto, CA; and Philadelphia, PA). This analysis included only caregivers who were the same race/ethnicity as the care recipients. All participants needed to have full information on study predictors and outcome (N=543).

Outcome Measures

This study focused on care recipient use of anxiolytic, antipsychotic, and antidepressant medications as the primary outcome measures. Information on medications was collected using the "brown bag" method of medication collection (38).

Accordingly, caregivers were asked to bring all currently administered medications to the in-person interview. Medication names were recorded by study personnel and assigned a therapeutic classification code (39). Although more detailed information on drug dosages and duration of use would have been desirable, these were not collected as the analysis of prescription medication was not a primary objective of the REACH II trial.

Predictors

Several caregiver and care recipient characteristics were examined as predictors of care recipient psychotropic medication use. Care recipient race, the focal variable of this study, was obtained through caregiver report and recorded as either non-Hispanic White, Hispanic/Latino, or Black/African American. Sampling was clustered by study site and was therefore also considered in the investigation. Other variables of interest reported by the caregiver included socioeconomic status as measured by current employment status (unemployed, retired, homemaker, employed), years of education, yearly household income before taxes, and income adequacy as measured by difficulty paying for basics (scores range from 1=not difficult at all to 4=very difficult).

Several care recipient characteristics were also used in this investigation and included baseline cognitive status as measured by the Mini-Mental State Examination (total scores range from 0 to 30, with higher scores indicating better cognitive functioning; scores less than or equal to 24 indicate cognitive impairment) (40); functional impairment as measured by the ability to independently perform basic and instrumental activities of daily living (ADLs and IADLs respectively; possible scores ranged from 0 to 14 with higher scores indicating more functional impairment) (41); and the number of behavioral disturbances exhibited in the past week as measured by the

Revised Memory and Behavior Problem Checklist (RMBPC) (scores range from 0-24 with higher scores indicating more problematic behaviors) (42).

No direct measure of pain was collected in REACH II; however, information on care recipient analgesic medication use was available. Previous research supports the use of analgesic medication as a proxy for pain (43) ; therefore, care recipient use of a narcotic or COX-2 inhibitor was utilized as a dichotomous surrogate for pain. Non-steroidal anti-inflammatory agents (NSAIDs) were not considered here as they have historically been used to manage low levels of chronic pain that cannot necessarily be eliminated (44). Additionally, NSAIDs such as aspirin are often used to decrease platelet aggregation and prevent blood clots (45). An overwhelming majority of the NSAID use in this study was aspirin (84.2%). Therefore, we focused on the presence of a narcotic or COX-2 inhibitor as surrogate for pain. Care recipient sex (male/female), age at baseline, and relationship to the caregiver (spouse/non-spouse) were also considered.

Several variables representing caregiver perceptions of caregiving were used in the analyses and included overall caregiving burden as measured by an abbreviated, 12-item version of the Zarit Caregiver Burden Inventory (total scores range from 0 to 48, with higher scores indicating greater burden) (46, 47); the extent to which a caregiver was bothered by assisting with care recipient functional limitations (daily care bother; final scores ranged from 0=not at all to 4=extremely) (48); the extent to which caregivers were bothered by care recipient problem behaviors (final scores ranged from 0=not at all to 4=extremely) (42); the amount of confidence caregivers had in handling the problem behaviors (final scores ranged from 0=not at all to 4=extremely) (42); caregiving mastery, assessed by eight items developed by REACH investigators (total scores ranged

from 0 to 16 with lower scores indicating greater mastery) (49); vigilance, measured by the hours per day a caregiver reported needing to be "on duty" to care for the care recipient (49); and positive aspects of caregiving, measured by the nine-item Positive Aspects of Caregiving Scale (total scores ranged from 0 to 36, with higher scores indicating more positive appraisals of the caregiving situation (50).

The final caregiver characteristics we considered were health and non-financial resources. Health was measured by self-report (both current and current versus six months previous; scores range from 0-5 with higher scores indicating poorer health) (51) and depression, as measured by the 10-item version of the Center for Epidemiological Studies-Depression Scale **(**CES-D), (scores range from 0 to 30, with higher scores indicating greater depressive symptomatology; scores of 16 or greater may indicate clinically significant depression) (52). Non-financial resources were captured by spiritual and religious coping resources and social network resources. Spiritual and religious coping was assessed by nine questions asking caregivers to rate the extent to which religious and spiritual beliefs affect their caregiving (total scores ranged from 0 to 18 with higher scores indicating greater spiritual and religious coping) (53); while multiple dimensions of social support including network size, support satisfaction, and negative social interactions were captured from several previous measures of social interaction and support (54-56). Social network size was assessed with two questions regarding the number of people who can be counted on to provide help. Total scores range from 0 to 10 with higher scores indicating larger social networks. Caregiver satisfaction with the help received from social contacts was assessed with three questions. Total scores range from 0 to 9, with higher scores indicating more satisfaction. Finally, the presence of

negative social interactions was assessed with four questions asking caregivers to rate the frequency of negative interactions on a four-point scale. Total scores ranged from 0-12 with higher scores indicating a greater frequency of negative social interactions. The final resource considered was dementia knowledge measured by the caregiver's general knowledge of memory loss, dementia, and end of life legal issues (total scores range from 0 to 4, with higher scores indicating greater knowledge of dementia and dementia related issues) (49).

Statistical Analysis

Descriptive statistics were computed for important demographic variables to provide a basic understanding of sample characteristics. To determine whether there were racial/ethnic disparities in the use of psychotropic medication, generalized linear models with a logit link function were fit using each medication as an outcome and race/ethnicity as a predictor. Two common methods used in the epidemiologic literature were considered for evaluating explanations for racial/ethnic disparities in psychotropic medication use, including successive addition of variables that may attenuate the effect of race and the addition of interaction terms to determine whether the risk of medication associated with a variable of interest differs across race.

For several reasons, these methods were considered insufficient for the current study. First, the explanatory variable sets in this investigation do not have a natural hierarchical structure, making it difficult to successively add variable sets that may explain the race effect. Second, two-way interactions with race in this context would, for example, provide information on whether the risk of medication associated with socio-economic status varies by race. The absence of an interaction, however, does not imply

that the effect of race is not explained by socioeconomic status. Racial/ethnic disparities in psychotropic medication may be due to differences in the distribution of socioeconomic status across race. Additionally, examining the interaction between race and socioeconomic status would require multiple interaction terms to account for the several variables that address socioeconomic status. Our study did not have enough power to evaluate two-way interactions between each potential explanatory variable and race. Consequently, we chose to address study hypotheses concerning differing patterns of medication use between racial/ethnic groups using AIC model selection, an information-theoretic approach presented by Burnham and Anderson (57). This approach allowed us to determine whether observed racial/ethnic disparities in psychotropic medication use could be explained by caregiver socioeconomic status, care recipient characteristics, caregiver perceptions of caregiving, caregiver health, or non-financial caregiving resources. Site was also considered due to the clustered nature of the sample. The AIC model selection approach has been used extensively in the ecology literature and has recently been recognized in the social sciences as a theoretically rigorous method for selecting an optimal model from various pre-specified models (58).

Briefly, this method uses Akaike Information Criterion (AIC) to quantify the amount of information in a given set of pre-specified models relative to the amount of noise. To facilitate comparison of models, AIC values are often rescaled such that the model with the minimum AIC has a value of zero. This model is the AIC minimal model and the most optimal. Remaining models are then ranked based on the rescaled AIC (lower is better) and compared to the minimum AIC model based on the differences in

AIC (Δ_{AIC}), with large values of Δ_{AIC} (typically greater than 2) providing little support for the non-minimal AIC model (57, 58).

Differences in model AIC can also be used to calculate the likelihood of a model given the data. These likelihoods represent the strength of evidence for each model. Typically, these likelihoods are normalized to be a set of positive Akaike weights that sum to one. Evidence ratios are then calculated from the weights by dividing the weight of a given model by the weight of the other model of interest. These ratios represent the relative strength of evidence for one model versus the other, and quantify the amount of variation in the selected best model from sample to sample if we could draw repeated, independent samples from the population. Evidence ratios close to one indicate that there is little evidence in favor of either model and suggests that we would observe a large amount of variation in the selected best model from sample to sample (57, 58).

Given our *a priori* interest in care recipient characteristics, caregiver socioeconomic status, caregiver perceptions of caregiving, caregiver health, and non-financial caregiving resources, we employed this approach to determine whether models containing some combinations of these variable sets without race were more parsimonious that the equivalent model containing race, thus implying that racial/ethnic disparities in psychotropic medication can be explained by these other factors. All combinations of variable sets were investigated in main effects models to determine whether certain sets contained relatively more information on the medication outcomes of interest.

Separate analyses were performed to investigate predictors of psychotropic medication use within racial/ethnic groups. For these analyses, data were stratified by

race and preliminary logistic regression models were used to examine the association between each predictor and the odds of medication use, while controlling for site, caregiver relationship to the care recipient, caregiver education, care recipient age, and care recipient sex. Predictors with a p-value less than or equal to 0.10 were retained for use in the next stage of the analysis because it would be otherwise unlikely that a covariate would contribute to a multivariable model. All predictors retained from the preliminary analyses were then included in multivariable models that also controlled for site, caregiver relationship to the care recipient, caregiver education, care recipient age, and care recipient sex. Income demonstrated a strong, positive correlation with education in each racial/ethnic group and was therefore not included as an additional confounder. Based on previous observations that predictors of psychotropic medication vary across medication type (16), analyses were performed separately for anxiolytics, antipsychotics, and antidepressants. Estimates from the multivariable models were considered statistically significant at the 5% level.

4.3 Results

Demographic characteristics of the REACH II participants are shown in Table 4.1. As shown in Table 4.2, care recipients across racial/ethnic groups exhibited, on average, approximately eleven behavioral disturbances, causing caregivers "a little" to "a moderate" amount of bother. On average, White and Black caregivers reported "very much" confidence managing behavioral disturbances whereas Hispanic caregivers reported only "moderate" levels of confidence. Figures 1 and 2 display the distribution of care recipient psychotropic medication use for each racial/ethnic group. As shown in Figure 4.1, antidepressants were the most prevalent psychotropic medication across all

racial groups, followed by antipsychotics, and anxiolytics. Within White/Caucasian care recipients the percentage of people taking an antipsychotic is slightly over two times the percentage taking an anxiolytic; however, that relation does not hold within Black/African American care recipients where the prevalence of anxiolytics is almost equal to that of antipsychotics. Within Hispanic/Latino care recipients, the prevalence of antipsychotic use is approximately 1.5 times greater than the use of anxiolytics.

The distribution of the number of psychotropic medications taken by care recipients is displayed in Figure 4.2. Hispanics demonstrate the lowest prevalence of psychotropic medication use with approximately 48% of care recipients receiving no psychotropic medication, followed by Whites at 40.30%. The percentage of Black care recipients using one, two, and three psychotropic medications is higher than Whites and Hispanics.

Between-Race Analysis

Logistic regressions analyses with each medication as an outcome and race/ethnicity as a predictor revealed that there were significant racial/ethnic disparities in the use of anxiolytics (Wald χ^2=7.89, df=2, p=0.02), with Black care recipients having significantly higher risk of anxiolytic use relative to White care recipients (OR=1.84, p<0.01). Significant racial/ethnic disparities were also observed for antipsychotics (Wald χ^2=5.85, df=2, p=0.05) with Hispanics having significantly lower risk of antipsychotic use versus Whites (OR=0.57, p=0.05). No significant racial/ethnic disparities in antidepressant use were observed, thus, no further investigation of between-race differences in antidepressant medication was performed.

The results of the AIC model selection process for anxiolytics and antipsychotics are presented in Tables 4.3 and 4.4 respectively. For both anxiolytics and antipsychotics, the top ten models contained approximately 90% of the total model weight, indicating that there was little need to examine combinations of variable sets contained in the lower-ranked models. Table 4.3 displays the AIC information for the top ten models predicting anxiolytics in direct comparison to the equivalent model with or without race. The model containing race alone and the model containing race with all sets of predictors are also shown for reference. Models are numbered by rank, with 1 being the most parsimonious. Recall that if a model without race is more parsimonious than the equivalent model containing race, racial/ethnic disparities in psychotropic medication can be explained by other variables in the model. Here, Model 1 accounts for over half of the model weight and contains care recipient race/ethnicity, in addition to the sets of variables representing perceptions of caregiving, and caregiver socioeconomic status. It is also worth noting that with the exception of Models 4 and 10, the top 10 models predicting anxiolytic medication contain race/ethnicity. This provides strong support for the importance of race/ethnicity in addition to other variables sets that predict medication use.

The evidence ratio comparing Model 1 to the same model without race/ethnicity (Model 4) is 14.38, indicating that, in repeated, independent samples from the population, Model 1 would be 14.38 times more likely to be selected as the best model versus the equivalent model without race. Thus, there is strong support for the inclusion of race in addition to perceptions of caregiving and socioeconomic status. It is also important to note that the model containing only race is ranked twenty-first and has a Δ_{AIC} of 11.32. This provides overwhelming evidence that race is an important predictor of care recipient

anxiolytic use cannot be adequately represented by caregiver and care recipient variables alone.

In the same way that the importance of race/ethnicity in anxiolytic medication use was evaluated, we can also examine the importance of other variables sets. For example, the difference between the top two models predicting anxiolytic use is the presence of socioeconomic status in Model 1. The evidence ratio comparing Model 1 to Model 2 is 6.00, indicating that there is considerably more support for the model containing socioeconomic status. Comparing Model 1 to a similar model without perceptions of caregiving (Model 6) shows substantially more support for the larger, AIC minimal model (evidence ratio 22.87).

Table 4.4 displays the AIC information for the top 10 models predicting antipsychotic medication in direct comparison to the equivalent model without race. Model 1, the AIC optimal model accounts for over half of the total model weight and includes race/ethnicity, study site, and care recipient characteristics. The equivalent model without race is ranked second with an evidence ratio of 3.01, indicating that there is approximately three times more evidence for the model containing race. This is much weaker evidence for the role of race/ethnicity than was observed for anxiolytics, and suggests that caregiver attributes may better explain racial/ethnic disparities in care recipient's use of anxiolytics versus antipsychotics.

Another notable difference between anxiolytic and antipsychotic medication is that study site appears in each of the top ten models for antipsychotic use. This indicates that there is substantial geographic variation across site that predicts antipsychotic medication. In fact, the evidence ratio comparing Model 1 to an equivalent model

without site (Model 26) is 462.89. Therefore, we have exceptionally strong evidence for the role of study site in predicting psychotropic medication use in this sample of community-dwelling dementia patients.

Within-Race Analysis

Anxiolytic medications were used by 28 White/Caucasian care recipients (14.14%), 41 Black/African American care recipients (23.30%), and 22 of Hispanic/Latino care recipients (13.02%). Among care recipients using an anxiolytic medication, 21.49% of White/Caucasians, 21.95% of Black/African Americans, and 13.64% of Hispanic/Latinos had concomitant antipsychotic use. Concomitant antidepressant use among anxiolytic users was observed in 17.85% of White/Caucasians, 26.83% of Black/African Americans, and 31.82% of Hispanic/Latinos.

Antipsychotics were used by 64 White/Caucasian care recipients (32.23%), 46 Black/African American care recipients (26.14%), and 36 Hispanic/Latino care recipients (21.30%). Among care recipients using an antipsychotic medication, 9.38% of White/Caucasians, 19.57% of Black/African Americans, and 8.33% of Hispanic/Latinos were also taking an antipsychotic. Concomitant antidepressant medication use was observed in 39.06% of White/Caucasian care recipients, 26.09% of Black African American care recipients, and 30.56% of Hispanic/Latino care recipients.

Antidepressants were used by 76 White/Caucasian care recipients (38.38%), 70 Black/African American care recipients (39.77%), and 53 Hispanic/Latino care recipients (31.36%). Among care recipients using antidepressant medications, 6.5% of White/Caucasians, 15.71% of Black/African Americans, and 13.21% of Hispanic/Latinos were also using an anxiolytic. Concomitant antipsychotic use was observed in 32.89% of

White/Caucasian care recipients, 17.14% of Black/African American care recipients, and 20.75% of Hispanic/Latino care recipients. All three psychotropic medications were used by 7 White/Caucasian care recipients (3.53%), 7 Black/African American care recipients (3.98%), and 1 Hispanic/Latino care recipient (0.59%).

Tables 4.5 through 4.7 display the results for the multivariable within-race analyses for Whites, Blacks, and Hispanics respectively. As shown in Table 4.5, there were significant differences in anxiolytic and antidepressant medication use by study site for White/Caucasian care recipients. Being a non-spousal caregiver was associated with an approximately 40% increased risk of anxiolytic medication; however, the results were not statistically significant (OR=1.40, p=0.63). As expected, increases in the frequency of problem behaviors and more behavioral bother was associated with an increased risk of medication (OR=1.02, p=0.30; OR=1.13, p=0.72 respectively), while perceiving more positive aspects of caregiving was protective (OR=0.97, p=0.28); however, these results did not achieve statistical significance.

Poor self-reported health measures were associated with an approximate 40% increase in antipsychotics and antidepressants by White/Caucasian care recipients (OR=1.41, p=0.09; OR=1.41, p=0.04); however, the results for antipsychotics were not statistically significantly associated with self-reported health. Increases in positive perceptions of caregiving and care recipient age were significantly associated with a decreased risk of antidepressant use (OR=0.97, 0.05; OR=0.97, p=0.04 respectively).

Final multivariable model results for psychotropic medication used by Black/African American care recipients are shown in Table 4.6. Although not statistically significant, increased difficulty paying for basics was associated with a

decrease in the use of both anxiolytics and antipsychotics (OR=0.70, p=0.08, OR=0.85, p=0.40). Increased confidence managing problem behaviors was associated with a decreased use of anxiolytics (OR=0.71 p=0.12) whereas increases in caregiving burden demonstrated a slight, positive association with medication use (OR=1.04, p=0.20); however, the estimates were not statistically significant.

Statistically significant associations were not observed for predictors of antipsychotic medication in Black/African American care recipients; however, the directions of observed associations between care recipient and caregiver characteristics and antipsychotic medication are as expected. For example, each additional functional impairment increased the risk of antipsychotic medication use by 4% (OR=1.04, p=0.64). Greater bother associated with providing assistance for functional impairments also increased the risk of antipsychotic medication use (OR=1.24, p=0.42).

Statically significant associations were observed for antidepressant use in Black/African American care recipients. Care recipient age was associated with a decreased risk of medication, which each additional year associated with a 5% reduction in antidepressant use (OR=0.95, p=0.02). The caregiver's use of spiritual and religious coping mechanisms also reduced the use of antidepressants by the care recipient (OR=0.91, p=0.05).

Table 4.7 displays the results from the final multivariable models predicting psychotropic medication use by Hispanic/Latino care recipients. As shown, no Hispanics were recruited at the Birmingham or Memphis study sites, and therefore analyses were limited to Philadelphia, Miami, and Palo Alto. Being a non-spousal caregiver and having poor self-reported health were the largest risk factors for care recipient anxiolytic use,

although the estimates were not statistically significant (OR=1.18 ,p=0.81; OR=1.44, p=0.12 respectively). Larger caregiver social networks decreased the risk of anxiolytic use, with each additional member decreasing the risk of care recipient anxiolytic use by 18% (OR=0.82, p=0.04).

The results for the Latino/Hispanic antipsychotic analysis are also presented in Table 4.7. In this analysis, study site was the strongest predictor of medication. The risk of antipsychotic medication was also increased by care recipient pain. Care recipients using a pain medication were 3.59 times more likely to also be using an antipsychotic compared to care recipients who were not receiving pain medication (OR=3.59, p=0.03). Finally, increasing caregiver satisfaction with social interactions was associated with more care recipient antipsychotic medication use (OR=1.20, p=0.02).

Finally, both caregiver and care recipient characteristics were significantly associated with antidepressant medication use in Hispanic/Latino care recipients. Higher levels of caregiver education and more negative social interactions were associated with decreases in antidepressants (OR=0.89 p=0.03; OR=0.84, p=0.02). Better care recipient cognitive functioning increased the risk of medication use (OR=1.08, p=0.01).

4.4 Discussion

This study utilized a diverse sample of community dwelling-dementia patients and their care recipients to examine racial/ethnic patterns of psychotropic medication use among demented adults living outside of formal care facilities. Comparing the prevalence of medication between care recipients from three different racial/ethnic groups, we observed significant disparities in the use of anxiolytic and antipsychotic medication use. To examine reasons for the observed disparities, we used AIC model

selection techniques to determine whether models containing some combinations of variable sets representing care recipient characteristics, caregiver socioeconomic status, caregiver perceptions of caregiving, caregiver health, and non-financial caregiving resources were more parsimonious than the equivalent model containing race, thus implying that racial/ethnic disparities in psychotropic medication can be explained by these other factors We also stratified by race/ethnic group to examine predictors of psychotropic medication within Whites, Blacks, and Hispanics, and found that aspects of caregiver social networks influence psychotropic medication in Hispanic/Latino care recipients but not in other racial/ethnic groups.

Contrary to study hypotheses, Black/African American Care recipients were almost twice as likely to use anxiolytic medication compared to White/ Caucasian care recipients. These results are in contrast to published work from cross-sectional and longitudinal studies of the Established Populations for Epidemiologic Studies of the Elderly (EPESE) cohort. Those works have consistently found higher rates of psychotropic medication use among community-dwelling, elderly Whites versus Blacks (19, 20, 59).

Given that White and Black care recipients demonstrated similar levels of impairment and behavioral disorders in our study, one potential explanation for these disparate findings may be the time period in which the studies were conducted. Data used in these studies were collected prior to the approval of rivastigmine, galantamine, and memantine (60). Limited choice of FDA approved medications to manage dementia would likely increase the off label use of psychotropic medication for dementia symptoms during the time period of the EPESE studies. Additionally, minority dementia

patients tend to receive a diagnosis later in the disease process compared to Whites, and once diagnosed, are less likely to access available treatment, which may have resulted in a higher prevalence of anxiolytic use among Whites (61). Data for REACH II, on the other hand, were collected during the release of three cholinesterase inhibitors and memantine, an NMDA receptor antagonist. Research has demonstrated racial/ethnic disparities in the use of new prescription drugs, with non-Hispanic Whites receiving more novel medications than non-Hispanic Blacks (62). Therefore, it is possible that the higher prevalence of anxiolytic use by Black/African American care recipients in this study is a result of White/Caucasian care recipients transitioning to newer, FDA approved medications.

We also found that Hispanic/Latino care recipients were approximately 40% less likely to use an antipsychotic medication than White/Caucasian care recipients. Previous studies of psychotropic medication use among community dwelling elderly did not detect a disparity in antipsychotic medication use (16, 18); however, our results are consistent with findings from studies of FDA approved anti-dementia medication (2, 3, 5) that found a higher prevalence of cholinesterase inhibitor use among White/Caucasian dementia patients versus Hispanic/Latinos. The discrepancy between our study and the null results from previous work may be due to differences in the study samples. The previous investigations of antipsychotics were performed in community-dwelling elders who may have been receiving antipsychotic medication for reasons unassociated with Alzheimer's and dementia. Those studies would not necessarily find a racial/ethnic disparity in antipsychotic medication if the disparity was strongest among elderly adults with dementia.

Results from the AIC model selection analyses revealed that racial/ethnic disparities in anxiolytic and antipsychotic medication use could not be adequately explained by caregiver and care recipient characteristics. This finding is commensurate with studies of cholinesterase inhibitors and NMDA receptor antagonists that found persistent inequalities after controlling for disease symptoms and social factors. For example, a recent study of dementia treatment among Medicare beneficiaries uncovered racial/ethnic disparities in medication use that could not be fully explained by demographic, economic, health status, access to health care, or health care utilization (5). Similarly, the racial/ethnic disparities observed by Hernandez *et al*. could not be accounted for by gender, age, education, marital status, clinical referral, severity, and racial composition of the community (2).

The finding of persistent racial/ethnic inequalities in medication used to treat dementia appears to be robust across FDA approved and non-approved medications, suggesting that there are still important explanations that have not been considered. One potential unexplored explanation is medication adherence. In a recent study of U.S. veterans with hypertension and dementia, Black and Hispanic patients demonstrated lower adherence to anti-hypertensive and anti-dementia medications relative to White patients (4). Another study of Medicaid patients found that after adjustment for income, Hispanics were more likely to avoid filling prescription due to cost, resulting in higher rates of cost-related non-adherence in Hispanic enrollees compared to Non-Hispanic enrollees (63). Therefore, it is possible that the racial/ethnic disparities in medication use observed in our study result from differing rates of adherence between the racial/ethnic groups. Participants in the REACH trials were asked to supply all currently used

medications, making it difficult to know whether absence of a medication represents non-adherence. Future studies investigating racial/ethnic disparities in psychotropic drug use among community-dwelling dementia patients should attempt to collect detailed information on prescribed medications, filled prescriptions, and medication routines in order to address issues of adherence. It is important to note, however, that this information should be used to increase adherence to medications that are deemed appropriate at the discretion of the physician.

Our investigation also examined the predictors of psychotropic medication separately for Whites, Blacks, and Hispanics. Although no clear patterns of predictors emerged for White or Black care recipients, analyses revealed that among Hispanic/Latino care recipients, larger social networks decreased the risk of anxiolytics, greater satisfaction with social support increased the risk of antipsychotics, and negative interactions with the social network were protective for antidepressants. This observation is consistent with a rich body of literature that identifies a more prominent role of extended social networks in the caregiving experience of Hispanic/Latino caregivers relative to White/Caucasian caregivers (35, 64, 65). It is important to acknowledge, however, that these extended networks do not necessarily provide more support than the networks of Non-Hispanic white caregivers, but rather serve as a key mediator between caregiving and health outcomes (25, 66).

Although investigating the mechanisms though which caregiver social support influence psychotropic medication use in the care recipient is beyond the scope of this paper, one plausible explanation may be found in the structure of Hispanic/Latino caregiving networks. Among this racial/ethnic group, medication is most often managed

by older caregivers (greater than 50 years of age); however, the average age of a Hispanic/Latino caregiver in the United States is approximately 42 years (67) It is therefore possible that positive interactions between a younger caregiver and an older member of the social network will increase the risk of medication for the care recipient. Future epidemiologic studies of community-dwelling dementia patients should make a special effort to recruit Hispanic/Latino caregiver/care recipient dyads and should collect information on caregiver social networks to better understand the mechanisms linking caregiver social support to care recipient medication outcomes in this growing population.

Our analysis also revealed pain as a significant predictor of antipsychotic medication use in Hispanic/Latino care recipients. Although we are the first study to report an association between pain and antipsychotic medication in community-dwelling Hispanic/Latinos with dementia, these results are consistent with reports of a positive association between pain and psychotropic medication among the greater population of dementia patients residing in the community (68, 69). It is possible that our findings reflect a practice of polypharmacy where narcotic-induced delirium is addressed with psychotropic medication (70); however it is also possible that, among Hispanics/Latinos, behavioral manifestations of pain are misinterpreted as dementia symptoms. The former explanation is supported by evidence that pain in Hispanics/Latinos is often undocumented in medical records and is subsequently undertreated (71). Refined analyses using self-reported pain when available or pain-related diagnoses are needed to unravel this issue.

The findings presented here should be evaluated within the context of the following limitations. First, the variable sets representing caregiver socioeconomic factors, care recipient characteristics, caregiver health, perceptions of caregiving, and non-financial resources were constructed using available data and subsequently, are not exhaustive. No formal examination of the extent to which variables within a set cluster together was made; however, all variables were chosen based on face validity and are reasonably expected to represent an important component of the variable set.

Another important limitation is that the AIC model selection method used to assess racial/ethnic disparities in psychotropic medication use depends on the models input by the user. The identified AIC optimal model is not the best from the universe of all possible models, but rather the best model from the ones chosen by the investigator. We based our choice of models on conceptual frameworks presented in the literature that outline determinants of psychotropic medication use in dementia caregiving and also how racial/ethnic disparities in medication use may arise. We chose to include only main effects models in our analysis because (1) a variable that explains racial/ethnic variations in medication use will not necessarily interact with race and (2) evaluating interactions between multiple variable sets would necessitate an extremely large number of interactions resulting in a prohibitively large number of models to evaluate. AIC model selection is not a test; therefore, p-values were purposefully omitted from model selection results.

Another limitation of this study concerns the construction of the racial/ethnic groups. In order to obtain sufficient sample size for an analysis of Hispanic/Latino care recipients, we combined Hispanic/Latino caregivers from different cultural subgroups,

largely Cuban and Mexican Americans. Despite speaking the same language, these people represent distinct cultural groups that may differ with respect to perceptions of caregiving and care recipient health outcomes (72). Additionally, we were unable to account for acculturation of the caregiver or care recipient. Previous research has shown differences in neuropsychological measures of cognition and caregiver perceptions of caregiving by levels of acculturation (73). Future studies should attempt to differentiate between different cultural groups and include acculturation measures whenever possible.

The lack of medication dose information available in REACH II is also a limitation of this study. The risk of adverse drug reactions increases at higher levels of medication intake. We were therefore limited in our ability to identify predictors of the riskiest treatment levels of psychotropic medication. Lack of dose information also restricted the extent to which we were able to identify racial/ethnic disparities in psychotropic medication use, as racial/ethnic minorities tend to receive higher doses of inappropriate medication (74).

REACH II data were collected before the release of the first FDA black box warning on the increased risk of death associated with antipsychotics in the elderly. Therefore, current dementia treatment patterns may differ from those observed here. Although we cannot specifically address this issues, a 2010 study by Dorsey *et al.* found that even after the release of the warnings, atypicals remained the most popular class of therapeutics among dementia patients, ranking second only to acetylcholinesterase inhibitors in each year of the study, suggesting that understanding the predictors of antipsychotic drug use in community-dwelling dementia patients is still a timely and important area of gerontological research (75). Unfortunately, results were reported

irrespective of race. An interesting area of future research would be to investigate whether the racial/ethnic disparities in psychotropic medication use observed here persisted after release of the black box warnings. Finally, it is important to note that REACH II was a randomized clinical trial and included individuals who were willing to participate in an intervention study. These people may not be representative of all community-dwelling dementia patients and their caregivers.

This study establishes a point of reference for evaluating racial and ethnic disparities in psychotropic medication use among dementia patients living in the community. To our knowledge, this is the first study to examine predictors of psychotropic medication among demented racial and ethnic minorities living outside of formal care facilities, and as a result, is the first study to identify the importance of Hispanic/Latino caregiver social networks in care recipient psychotropic medication use. Additionally, our results highlight the need for better pain management strategies specifically among Latino community-dwelling elderly with dementia.

In conclusion, this study suggests that there are racial/ethnic disparities in the use of psychotropic medication by community-dwelling dementia patients and that social networks play a key role in Latino/Hispanic care recipient medication use. These findings suggest that for Hispanics/Latinos, interventions aimed at improving communication between family members and other members of the social network may change care recipient medication use, although the extent to which psychotropics are appropriate is left to the discretion of the physician. This work also provides valuable information to clinicians about the association between pain and psychotropic medication use. More diligent evaluation and treatment of pain symptoms among Hispanic/Latino

dementia patients may be a reasonable strategy for reducing antipsychotic medication and improving patient quality of life.

4.5 Supplemental Equations

The following equation is a mathematical representation of the general linear models used to assess study hypotheses (76).

$$logit\ (\pi_i) = \ \alpha + \beta x_i + e_i$$

Where π_i is the probability of medication for the i[th] care recipient. The errors, e_i are assumed to follow a normal distribution $\sim N(0, \sigma^2)$.

The tools used to compare the i[th] model to the AIC minimal (AIC_{min}) model in Tables 4.4 and 4.5 can be calculated with the following formulas (58).

$$\Delta_i = AIC_i - AIC_{min}$$

$$Weight_i = \frac{exp^{\frac{-\Delta_i}{2}}}{\sum_{r=1}^{R} exp^{\frac{-\Delta_r}{2}}}$$

Where i=1,2,3,….R.

$$Evidence\ ratio_{(AIC_{min},i)} = \frac{Weight_{AIC\ min}}{Weight_i}$$

Table 4.1 Demographic Characteristics of Study Participants*

	White/Caucasian		Black/African American		Hispanic/Latino	
Demographics	Caregiver	Care recipient	Caregiver	Care recipient	Caregiver	Care recipient
Age, years†	59.98 (12.68)	77.84 (10.26)	62.28 (12.82)	79.78 (8.41)	58.79 (14.12)	79.80 (8.98)
Sex, n (%)†						
Female	161 (81.31)	101 (51.01)	149 (84.66)	110 (62.50)	136 (80.47)	113 (66.86)
Male	37 (18.69)	97 (48.99)	27 (15.34)	66 (37.50)	33 (19.53)	56 (33.14)
Employment Status, n (%)§						
Unemployed	19 (9.60)	-	20 (11.36)	-	20 (11.83)	-
Retired	92 (46.46)	-	64 (36.36)	-	51 (30.18)	-
Homemaker	32 (16.16)	-	30 (17.05)	-	41 (24.26)	-
Employed	55 (27.78)	-	62 (35.43)	-	57 (33.73)	-
Years of Education§	13.78 (1.96)	-	13.05 (2.14)	-	11.04 (3.95)	-
Household Income§	46,161.15 (25,026.24)	-	31,718 (22,382.91)	-	25,783.54 (21,750.45)	-
Income Adequacy	1.72 (1.02)	-	1.66 (1.06)	-	1.47 (1.00)	-
Relationship to care recipient, n(%)§						
Spouse	111 (56.06)	-	52 (29.55)	-	62 (36.69)	-
Non-spouse	87 (43.94)	-	124 (70.45)	-	107 (63.31)	-
Years caring for care recipient	3.98 (5.54)	-	3.99 (3.96)	-	6.22 (9.34)	-

* All values are presented as means and standard deviations, except where otherwise noted

† $p \leq 0.05$ for chi-square test of homogeneity for care recipient variable

§ $p \leq 0.05$ for chi-square test of homogeneity (discrete variable) or ANOVA (continuous variable) for caregiver variable

Table 4.2 Descriptive Statistics for Study Predictors and Outcomes

Study Predictors and Outcomes	Range*	White/Caucasian Mean (SD)	Black/African American Mean (SD)	Hispanic/Latino Mean (SD)
Care recipient attributes				
Cognitive status	0-30	11.61 (7.38)	12.62 (7.68)	12.78 (6.92)
Functional impairment	0-14	10.43 (2.80)	10.39 (2.84)	9.63 (3.39)
Number of problem behaviors endorsed	0-24	10.56 (4.11)	10.70 (4.04)	10.67 (3.83)
Pain, n (%)	-	22 (11.11)	30 (17.05)	17 (10.06)
Caregiver attributes				
Self-reported health				
Overall current health	0-4	2.10 (1.01)	2.06 (1.05)	2.24 (1.08)
Overall current health compared to 6 months previous	0-4	2.06 (0.81)	2.10 (0.91)	2.27 (0.84)
Caregiver depression	0-60	9.58 (6.35)	9.66 (6.41)	10.75 (6.58)
Caregiver burden	0-48	16.88 (8.67)	17.03 (8.73)	17.81 (9.11)
Daily care bother	0-4	0.73 (0.76)	0.81 (0.83)	0.76 (0.77)
Problem behavior bother	0-4	1.42 (0.89)	1.56 (0.93)	1.44 (0.88)
Problem behavior confidence	0-4	2.19 (0.90)	2.04 (0.93)	1.91 (0.93)
Mastery	0-6	5.93 (2.70)	6.32 (2.96)	5.65 (2.94)
Vigilance	0-24	18.86 (6.70)	19.82 (6.24)	19.33 (6.95)
Positive aspects of caregiving	0-36	24.74 (8.93)	26.09 (8.82)	26.08 (8.70)
Spiritual and religious coping	0-18	15.22 (3.20)	15.13 (3.39)	13.95 (3.81)
Social Network				
Social network size	0-10	6.70 (2.31)	6.63 (2.28)	5.90 (2.29)
Social support satisfaction	0-9	5.31 (2.58)	5.51 (2.86)	4.17 (2.82)
Negative social interaction	0-12	2.71 (2.57)	2.93 (3.03)	3.07 (2.78)
Dementia knowledge	0-4	2.93 (1.30)	2.24 (1.26)	1.90 (1.35)

Table 4.2 continued

Study Predictors and Outcomes	Range	White/Caucasian Mean (SD)	Black/African American Mean (SD)	Hispanic/Latino Mean (SD)
Outcomes, n (%)				
Anxiolytics[†]	-	28 (13.93)	41 (23.30)	22 (12.94)
Antipsychotics[†]	-	65 (32.34)	46 (26.14)	36 (21.18)
Antidepressants	-	77 (38.31)	73 (39.77)	54 (31.76)

[*]Indicates range of the measurement instrument
[†]$p \leq 0.05$ for chi-square test of homogeneity
[§] $p \leq 0.05$ for ANOVA

Table 4.3 AIC Model Fit Information for Models Predicting Care Recipient Anxiolytic Use

Model Rank	Variable Set Included in the Model*							AIC	Δ_{AIC}	Weight	Rank of Equivalent Model Without Race	Evidence Ratio†
	Care Recipient Race/Ethnicity	Site	A	B	C	D	E					
1	1	0	0	0	1	0	1	477.85	0.00	0.58	4	14.38
2	1	0	0	0	1	0	0	481.83	3.98	0.08	10	6.00
3	1	0	0	1	1	0	1	483.16	5.31	0.04	21	16.97
:												
5	1	0	1	0	1	0	1	483.32	5.47	0.04	17	8.02
6	1	0	0	0	0	0	1	483.83	5.98	0.03	35	22.87
7	1	0	0	0	1	1	1	483.99	6.14	0.03	22	11.78
8	1	0	0	1	0	0	1	484.26	6.41	0.02	42	25.85
9	1	1	0	0	1	0	1	484.58	6.73	0.02	40	20.79
:												
21	1	0	0	0	0	0	0	489.32	11.32	<0.01	NA	NA
:												
110	1	1	1	1	1	1	1	499.74	21.89	<0.01	125	11.95

*Inclusion in the model is indicated by 1, exclusion is indicated by 0

Set A includes care recipient variables (cognitive impairment, functional impairment, problem behavior frequency, pain, relationship to the caregiver, sex, and age

Set B includes caregiver health variables (self reported health both current and current compared to six months previous, and depression)

Set C includes perceptions of caregiving (caregiving burden, bother assisting with functional impairments, bother handling problem behaviors, confidence handling problem behaviors, caregiving mastery, vigilance, and positive aspects of caregiving)

Set D includes non-financial caregiving resources (spiritual and religious coping, social network size, social network satisfaction, negative social interaction, and dementia knowledge

Set E includes caregiver socioeconomic status (education, employment, income, and income adequacy)

†Evidence ratio comparing model with race to an equivalent model without race

Table 4.4 AIC Model Fit Information for Models Predicting Care Recipient Antipsychotic Use

Model Rank	Variable Set Included in the Model*							AIC	Δ_{AIC}	Weight	Rank of Equivalent Model With or Without Race	Evidence Ratio†
	Care Recipient Race/Ethnicity	Site	A	B	C	D	E					
1	1	1	1	0	0	0	0	616.26	0.00	0.51	2	3.03
:												
3	1	1	1	1	0	0	0	619.29	3.03	0.11	4	3.88
:												
5	1	1	0	0	0	0	0	622.49	6.23	0.02	15	3.85
6	1	1	1	0	0	1	0	622.94	6.69	0.02	12	1.78
:												
9	1	1	1	0	1	0	0	623.35	7.09	0.01	16	2.59
10	1	1	1	0	0	0	1	623.88	7.62	0.01	7	0.65
:												
41	1	1	1	0	1	0	1	630.91	14.65	<0.01	8	0.02
:												
50	1	0	0	0	0	0	0	632.21	16.21	<0.01	NA	NA
:												
82	1	1	1	1	1	1	1	636.41	20.16	<0.01	67	0.33

*Inclusion in the model is indicated by 1, exclusion is indicated by 0

Set A includes care recipient variables (cognitive impairment, functional impairment, problem behavior frequency, pain, relationship to the caregiver, sex, and age

Set B includes caregiver health variables (self reported health both current and current compared to six months previous, and depression)

Set C includes perceptions of caregiving (caregiving burden, bother assisting with functional impairments, bother handling problem behaviors, confidence handling problem behaviors, caregiving mastery, vigilance, and positive aspects of caregiving)

Set D includes non-financial caregiving resources (spiritual and religious coping, social network size, social network satisfaction, negative social interaction, and dementia knowledge

Set E includes caregiver socioeconomic status (education, employment, income, and income adequacy)

†Evidence ratio comparing model with race to an equivalent model without race

Table 4.5 Predictors of Psychotropic Medication for White/Caucasian Care Recipients

Variable	Anxiolytics		Antipsychotics		Antidepressants	
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Site						
Philadelphia	REF	-	REF	-	REF	-
Birmingham	2.42	(0.44, 13.19)	1.35	(0.54, 3.39)	2.63	(1.01, 6.82) †
Memphis	1.25	(0.20, 7.66)	0.64	(0.24, 1.67)	0.67	(0.24, 1.84)
Miami	6.44	(1.17, 35.40)†	1.52	(0.51, 4.53)	1.13	(0.36, 3.53)
Palo Alto	2.65	(0.45, 15.61)	0.48	(0.15, 1.48)	0.87	(0.29, 2.61)
Care recipient attributes						
Sex						
Female	REF	-	REF	-	REF	-
Male	2.86	(0.70, 11.71)	0.54	(0.23,1.25)	1.28	(0.54, 3.06)
Age at baseline	1.00	(0.95, 1.05)	0.99	(0.96, 1.02)	0.97	(0.94, 0.99) †
Functional impairment					1.12	(0.98, 1.26)
Problem behavior frequency	1.02	(0.98, 1.07)				
Caregiver attributes						
Education	1.08	(0.85, 1.37)	1.10	(0.93, 1.31)	0.99	(0.84, 1.17)
Income adequacy						
Relationship to care Recipient						
Spouse	REF	-	REF	-	REF	-
Non-Spouse	1.38	(0.35, 5.47)	0.64	(0.28, 1.47)	1.04	(0.45, 2.41)
Self-reported health						
Overall current health					1.41	(1.02, 1.96)†
Overall current health compared to 6 months previous			1.41	(0.94, 2.09)		
Caregiver depression	1.05	(0.97, 1.14)				
Caregiver burden	1.01	(0.93, 1.09)				
Problem behavior bother	1.13	(0.58, 2.23)				
Positive aspects of caregiving	0.97	(0.91, 1.02)			0.97	(0.93, 0.99)†

*Estimates from logistic regression model controlling for site, care recipient sex, age at baseline, caregiver relationship to the care recipient, and income adequacy

†$p \leq 0.05$

Table 4.6 Predictors of Psychotropic Medication for Black/African American Care Recipients

Variable	Anxiolytics		Antipsychotics		Antidepressants	
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Site						
Philadelphia	REF	-	REF	-	REF	-
Birmingham	1.10	(0.32, 3.76)	1.45	(0.49, 4.29)	1.45	(0.52, 4.00)
Memphis	1.91	(0.35, 4.09)	0.43	(0.13, 1.14)	2.05	(0.73, 5.74)
Miami	1.20	(0.31, 4.66)	0.73	(0.20, 2.65)	0.53	(0.15, 1.84)
Palo Alto	0.34	(0.05, 2.16)	0.61	(0.12, 3.08)	1.04	(0.27, 3.97)
Care recipient attributes						
Sex						
Female	REF	-	REF	-	REF	-
Male	0.79	(0.31, 2.03)	0.66	(0.26, 1.66)	1.05	(0.47, 2.33)
Age at baseline	1.00	(0.95, 1.05)	0.98	(0.93, 1.03)	0.95	(0.91, 0.99) †
Cognitive status			0.95	(0.90, 1.00)		
Functional impairment			1.04	(0.89, 1.22)		
Problem behavior frequency	1.00	(0.96, 1.05)				
Caregiver attributes						
Education	1.08	(0.89,1.31)	1.01	(0.83, 1.22)	1.01	(0.85, 1.19)
Income adequacy	0.70	(0.47, 1.04)	0.85	(0.59, 1.24)		
Relationship to care Recipient						
Spouse	REF	-	REF	-	REF	-
Non-Spouse	0.65	(0.24, 1.80)	1.37	(0.50, 3.75)	1.19	(0.50, 2.82)
Self-reported health						
Overall current health	1.41	(0.93, 2.16)				
Caregiver depression	0.96	(0.88, 1.05)	1.01	(0.94, 1.09)		
Caregiver burden	1.40	(0.98, 1.10)	1.01	(0.96, 1.08)		
Functional impairment bother			1.24	(0.73, 2.11)		
Problem behavior confidence	0.71	(0.46, 1.10)				
Vigilance	1.01	(1.00, 1.18)	1.07	(0.99, 1.15)		
Spiritual and religious coping					0.91	(0.82, 1.00) †

*Estimates from logistic regression model controlling for site, care recipient sex, age at baseline, caregiver relationship to the care recipient, and income adequacy

†$p \leq 0.05$

Table 4.7 Predictors of Psychotropic Medication for Hispanic/Latino Care Recipients

Variable	Anxiolytics		Antipsychotics		Antidepressants	
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Site						
Philadelphia	REF	-	REF	-	REF	-
Birmingham	-	-	-	-	-	-
Memphis	-	-	-	-	-	-
Miami	1.16	(0.27, 4.99)	9.27	(2.07, 41.48)†	1.51	(0.51, 4.44)
Palo Alto	0.83	(0.19, 3.59)	1.98	(0.42, 9.21)	0.98	(0.34, 2.83)
Care recipient attributes						
Sex						
Female	REF	-	REF	-	REF	-
Male	1.45	(0.42, 5.02)	1.38	(0.43, 4.42)	1.43	(0.55, 3.72)
Age at baseline	0.97	(0.92, 1.03)	1.03	(0.97, 1.08)	0.98	(0.94, 1.02)
Cognitive status			0.97	(0.91, 1.04)	1.08	(1.02, 1.14)†
Functional impairment			1.14	(0.98, 1.33)		
Pain						
No	REF	-	REF	-	REF	-
Yes	1.04	(0.21, 5.27)	3.59	(1.12, 11.52)†	2.48	(0.77, 7.97)
Caregiver attributes						
Education	1.00	(0.88, 1.15)	0.98	(0.87, 1.10)	0.89	(0.80, 0.99)†
Income adequacy					1.16	(0.79, 1.70)
Relationship to care recipient						
Spouse	REF	-	REF	-	REF	-
Non-Spouse	1.18	(0.31, 4.56)	1.79	(0.54, 5.93)	2.00	(0.70, 5.76)
Self-reported health						
Overall current health	1.44	(0.91, 2.27)				
Problem behavior bother			0.77	(0.48, 1.25)	1.46	(0.93, 2.28)
Positive aspects of caregiving					0.98	(0.93, 1.02)

Table 4.7 continued

Variable	Anxiolytics		Antipsychotics		Antidepressants	
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Social network						
Social network size	0.82	(0.67, 0.99)†				
Social support satisfaction			1.20	(1.03, 1.41) †		
Negative interaction					0.83	(0.72, 0.98)†

*Estimates from logistic regression model controlling for site, care recipient sex, age at baseline, caregiver relationship to the care recipient, and income adequacy
†$p \leq 0.05$

Figure 4.1 Care Recipient Psychotropic Medication Prevalence by Race/Ethnicity

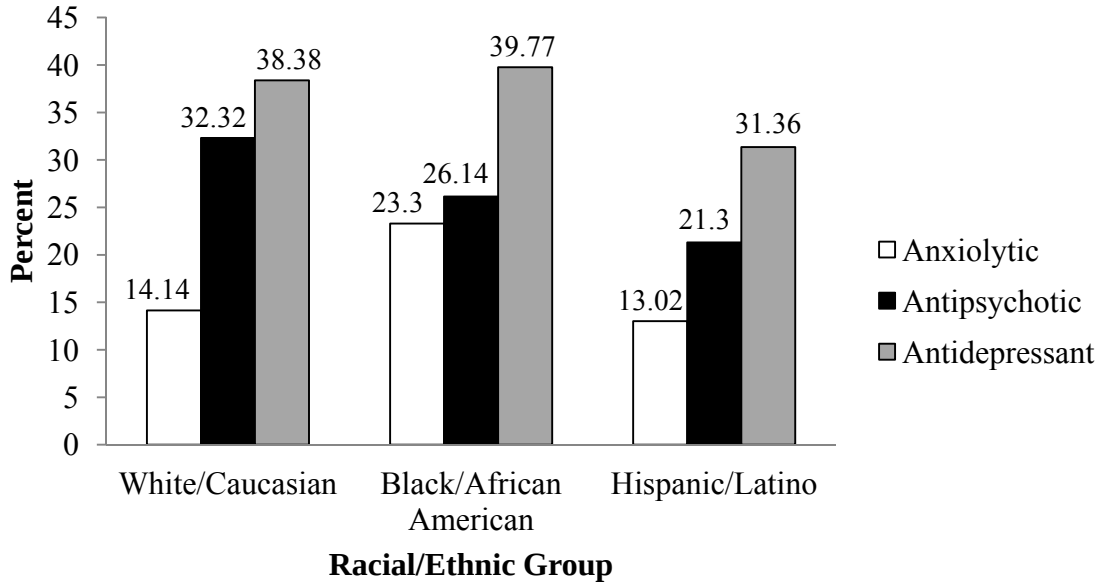
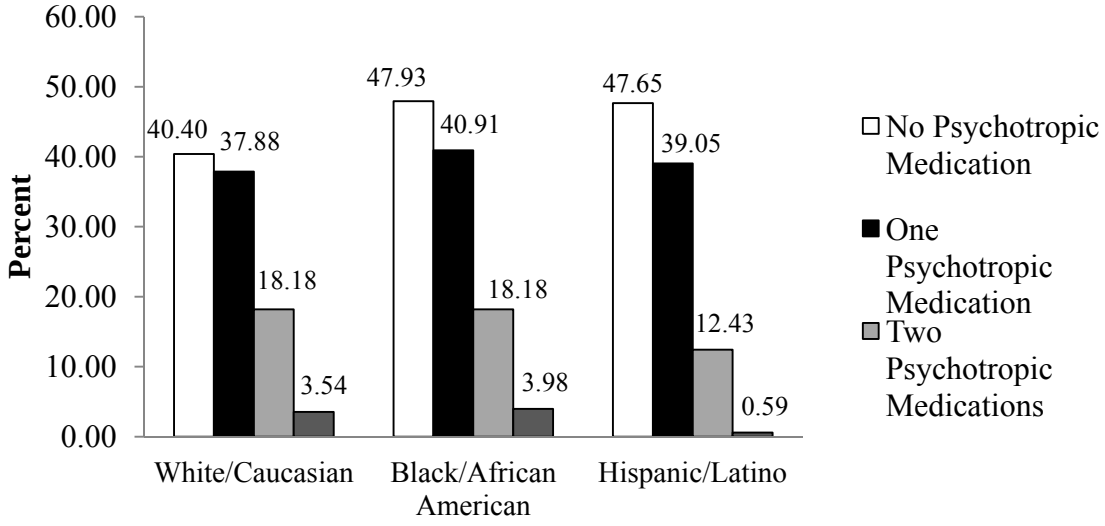


Figure 4.2 Number of Care Recipient Psychotropic Medications by Race/Ethnicity



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Chapter 5

Conclusions

Dementia is one of the most devastating and challenging diseases facing society today. Although cognitive decline is often referred to as the hallmark symptom of dementia, behavioral and psychological symptoms are highly prevalent over the course of disease (1). These symptoms are often unpredictable and complicate care, and are a legitimate focus for pharmacologic intervention; however, unlike cognitive dementia symptoms, there are currently no approved medications for the treatment of dementia-related behavioral disturbances. Psychotropic medications, antipsychotics in particular, have filled this niche without an approved dementia indication for over fifty years. Recent negative safety findings combined with reports of modest efficacy bring this practice into question suggesting that the potential benefits may be outweighed by the substantial risks (2).

Most studies of psychotropic medication use in dementia patients have focused on patients residing in formal care facilities, with little attention paid to dementia patients residing in the community (3-6). This dissertation adds to the current literature by investigating cross-sectional and longitudinal predictors of psychotropic medication use in racially and ethnically diverse populations of community-dwelling dementia patients and their caregivers. Understanding the predictors of psychotropic medication use in community-dwelling dementia patients will help researchers develop interventions aimed

at reducing unsafe use of these medications and may potentially help guide health care policy, particularly related to clinical practice and education.

5.1 Summary of findings

Chapter 2 presents a cross-sectional study examining the predictors of psychotropic medication use, going beyond traditional behavioral risk factors and including caregiver perceptions of caregiving and care recipient pain in order to obtain a comprehensive understanding of the patterns of psychotropic medication use in community-dwelling elderly with dementia. Using a racially diverse sample of Alzheimer's patients and their informal caregivers, we found that the prevalence of care recipient psychotropic medication use among dementia patients living in the community was comparable to that observed in nursing homes (4), with over half of care recipients using at least one anxiolytic, antipsychotic, or antidepressant medication.

Similar to studies of traditional risk factors, our findings revealed that more problematic behaviors were significantly associated with increased odds of anxiolytic medication (7, 8). Importantly though, this association was only observed in bivariate analyses and did not remain when caregiver attributes were included in multivariable analyses. Increases in caregiver confidence managing problem behaviors was statistically significantly associated with a decreased risk of anxiolytic medication use, suggesting that caregiver confidence may be an important target for interventions aimed at reducing the use of anxiolytic medication by elderly dementia patients living in the community.

The other major finding of Chapter 2 was the strong association between care recipient pain and the use of antipsychotic medication. Many times, dementia patients

are unable to verbally report pain, and as a result, act out in ways that can be misinterpreted as neurological symptoms of dementia (9, 10). This research suggests that treatment of behavioral disturbances with antipsychotic medication may actually be misguided efforts at addressing pain.

To our knowledge, this is the first study to investigate caregiver and care recipient characteristics of psychotropic medication use among demented adults living in the community. The risk of serious adverse events associated with the use of these medications by patients with dementia emphasizes the importance of identifying potentially modifiable risk factors for medication use. This study supports that effort by focusing on a relatively understudied group of dementia patients and expanding the current scope of potential risk factors to include care recipient pain and informal caregiver characteristics.

The study presented in Chapter 3 extends the work presented in Chapter 2 by examining the longitudinal association between caregiver perceptions of caregiving, dementia patient symptoms, and the risk of care recipient psychotropic medication to determine whether the risk of medication changes over time as health declines and the risk of adverse drug events increase. Prior to conducting this comprehensive analysis, we first evaluated whether caregiver participation in the REACH I six-month intervention designed to reduce caregiver burden and depression influenced psychotropic medication in the care recipient during the intervention period. This preliminary analysis revealed that intervention was not associated with changes in care recipient psychotropic medication use.

Similar to the results in Chapter 2, our main analysis found that caregiver and care recipient characteristics are important predictors of care recipient psychotropic medication use. Again, more problematic behaviors were significantly associated with increased odds of anxiolytic medication in bivariate analyses; however, the association was no longer significant when modeled together with caregiver attributes. Unfortunately, caregiver confidence managing problematic behaviors was not available in this dataset, making a direct comparison to results presented in Chapter 2 difficult. This study, however, found that caregiver bother managing problem behaviors was the strongest predictor of care recipient anxiolytic medication use. Taken together with the results from Chapters 2, these findings suggest that caregiver efficacy and bother associated with problematic behaviors may be important targets for interventions aimed reducing anxiolytic use in community-dwelling elderly with dementia.

Another important finding of this study was the varying association between care recipient functional impairment and antipsychotic use over time. We found that care recipient functional impairment was associated with an increased risk of antipsychotic medication; however, the association was significantly attenuated over time. This finding may explain why previous investigations have failed to detect an association between functional impairment and antipsychotic medications (11) and suggests that strategies to reduce antipsychotic medication use in community-dwelling dementia patients may need to change over the course of disease.

We believe that this is the first study to evaluate longitudinal predictors of psychotropic medication in community-dwelling dementia patients. Although the REACH I caregiver intervention was not associated with changes in care recipient

medication use in this study, the work contained in Chapters 2 and 3 provides valuable information for the development of future interventions. Specifically, our studies suggest that increasing caregiver efficacy and reducing bother associated with care recipient problem behaviors may be a reasonable strategy for decreasing anxiolytic drug use among community-dwelling dementia patients while also improving caregiver quality of life. Furthermore, intervention strategies to reduce antipsychotic use will likely need to change over the course of disease to account for the fluctuation of medication risk factors over time.

To accomplish this, we recommend that psychotropic minimization efforts focus on training caregivers to recognize the signs of frustration and negative thought patterns and teaching strategies for modifying negative thoughts. Additionally efforts should be directed towards educating caregivers on dementia caregiving skills and helping them achieve mastery of the skills demanded by their caregiving situation. This includes modeling caregiving behaviors; providing feedback and encouragement; and helping caregivers identify and solicit help. These comprehensive strategies have been shown to increase efficacy and decrease bother associated with problem behaviors in spousal caregivers of dementia patients. The improvement in caregiver appraisals was also observed to persist over time as treatments were sensitive to changes in caregiver needs as caregiving responsibilities transitioned from managing problem behaviors to assisting with functional impairments (12).

The final study of this dissertation, presented in Chapter 4, examines patterns of psychotropic medication use both within and between community-dwelling dementia patients from three different racial/ethnic groups. Given the documented racial/ethnic

disparities in FDA approved anti-dementia medications (13-16), we hypothesized that the prevalence of psychotropic medication would be higher in non-Hispanic Whites compared to Hispanics/Latinos or Black/African Americans. In our study however, Black care recipients had a higher risk of anxiolytic medication use relative to Whites. This finding was in contrast to several previous works that found higher rates of psychotropic medication in non-Hispanic Whites versus non-Hispanic Blacks (17-19). A potential explanation for this discrepancy may be the time period in which the data were collected. The participants in this analysis were recruited during the release of three cholinesterase inhibitors and memantine, an NMDA receptor antagonist. Therefore, the higher prevalence of anxiolytic use in Black/African Americans may be the result of White/Caucasian care recipients transitioning to newer, FDA approved medications more quickly than Black/African American care recipients FDA. This hypothesis could be tested using data from the Medicare Current Beneficiary Survey (MCBS), a continuous sample of Medicare recipients conducted by the Centers for Medicare and Medicaid Services. Participants in the MCBS are asked a battery of questions relating to demographics, health status, health care utilization, and insurance coverage. Information from the MCBS can be linked to claims data containing diagnostic indicators, prescription fills, and payment information (16). Using the MCBS, a retrospective cohort analysis of community-dwelling dementia patients could be undertaken to determine if the risk of anti-dementia medications associated with race/ethnicity changes over time. Time plots and interaction plots could be used to visually examine the trends of medication use over time by race and would provide evidence that Black/African

American dementia patients transitioned to FDA approved anti-dementia medications at a slower rate than White/Caucasian patients.

In efforts to better understand the observed disparities in psychotropic medication use, we used AIC model selection methods to determine whether racial/ethnic disparities in psychotropic medication could be explained by sets of variables representing socioeconomic status, care recipient characteristics, caregiver perceptions of caregiving, caregiver health, and non-financial caregiving resources. These analyses revealed that racial/ethnic disparities in psychotropic medication use could not be adequately explained by caregiver and care recipient characteristics. This finding is commensurate with studies of cholinesterase inhibitors and NMDA receptor antagonists that found persistent inequalities after controlling for disease symptoms and social factors (13, 16), suggesting that observed disparities in medication use may be attributable to cultural attitudes towards health care and medication (20) or health care biases in prescribing treatment that is not commonly measured in studies of community-dwelling dementia patients and their caregivers. Future studies should attempt to collect information on informal dementia caregiver attitudes towards health care and current dementia treatment options. Studies focusing on physicians, the most frequent prescribers of psychotropic medication (21) should also be conducted to identify opportunities for modifying biases that result potentially dangerous prescription patterns.

The final goal of this study was to address the lack of published literature regarding the predictors of psychotropic medication within minority, community-dwelling, dementia patients. To that end, we examined predictors of psychotropic medication within White, Black, and Hispanic dementia patients. Although no clear

pattern of predictors emerged for White or Black care recipients, aspects of social networks were significantly associated with the use of anxiolytics, antipsychotics and antidepressants within Hispanic/Latino care recipients. These results are consistent with a rich body of literature that finds extended social networks to be particularly important to Hispanic/Latino caregivers relative to White/Caucasian caregivers (22, 23), but are the first to identify social networks as a determinant of dementia patient psychotropic medication use.

5.2 Limitations and Strengths

Some important limitations of this research need to be considered when evaluating the results presented herein. First, all study hypotheses were evaluated using data obtained from REACH intervention participants and may not be generalizable to the population of dementia patients living in the community. For example, eligible caregivers for the REACH trials needed to have provided care for at least six months and be the primary caregiver involved with daily care tasks and other caregiving responsibilities. Additionally, it is reasonable to expect that interventions aimed reducing caregiver burden and improving caregiver quality of life would attract caregivers most in need of intervention services. These selection biases likely explain the relatively high levels of care recipient impairment and caregiver burden exhibited in the REACH data. Consequently, the associations observed in these studies may not apply to newer caregivers of patients with recently diagnosed disease. The narrow selection of study participants and limited follow-up period may have also hindered our ability to detect changes in predictors of medication use over time. As discussed in Chapter 3, enrolling patients at various stages of dementia and increasing follow-up time may have increased

our ability to detect changes in anxiolytic use and may have also revealed a more pronounced association between functional impairment and antipsychotics.

Another limitation of this research concerns the lack of medication dosing information available in REACH. The risk of adverse drug reactions increases at higher levels of medication intake. We were therefore limited in our ability to identify predictors of the riskiest treatment levels of psychotropic medication. Lack of dose information also restricted the extent to which we were able to identify racial/ethnic disparities in psychotropic medication use, as racial/ethnic minorities tend to receive higher doses of inappropriate medication (24).

An additional limitation of the racial/ethnic disparities work presented in Chapter 3 relates to the construction of the racial/ethnic groups. This investigation combined Hispanic/Latino caregivers from different cultural subgroups. A majority of the REACH Hispanic/Latino participants were Cuban and Mexican Americans. Despite speaking the same language, these people represent distinct cultural groups that may differ with respect to perceptions of caregiving and care recipient health outcomes (25). We were also unable to account for acculturation of the caregiver or care recipient. Consequently, we may be missing an important predictor of psychotropic medication use as previous research has shown differences in neuropsychological measures of cognition and caregiver perceptions of caregiving by levels of acculturation (26).

Lastly, REACH data were collected before the release of the first FDA black box warning on the increased risk of death associated with antipsychotics in the elderly. Therefore, current dementia treatment patterns may differ from those observed in our study. As discussed in previous chapters; however, psychotropic medication, particularly

antipsychotics are still widely used in people with dementia (27), indicating that understanding the predictors of psychotropic drug use in community-dwelling dementia patients is still a timely and important area of gerontological research.

Nonetheless, this dissertation has many strengths, most notably, the rich data source used for each analysis. The REACH studies were designed to assess caregiver interventions, and as a result, contain a reasonably large, diverse, sample that is well-described from a caregiver perspective. In addition to information about informal caregivers, REACH also collected information on community-based psychotropic medication use. Using this unique data source allowed us to be the first investigators to examine caregiver and care recipient characteristics as predictors of psychotropic medication use in community-dwelling dementia patients both cross-sectionally, and over time.

Another advantage of the REACH data is the inclusion of participants from three different racial/ethnic groups. The large number of Whites, Blacks, and Hispanics allowed us to examine racial/ethnic disparities in psychotropic medication use and also enabled us to identify medication risk factors within each racial/ethnic group separately. This is an important improvement from previous research that tended to dichotomize race into White/Non-White categories (11).

5.3 Future Research Directions

The risks associated with psychotropic drug use in people with dementia are well-established (2). Antipsychotics in particular carry substantial risks including death, and consequently should only be used as a last resort, when all other attempts to manage symptoms have failed. In order to have reasonable non-pharmacologic alternatives, it is

imperative to understand the context in which psychotropic medication is used. A majority of the work examining psychotropic medication use in dementia patients focuses on the formal care setting, with very little attention paid to patients living in the community (3-6). The conclusions drawn from nursing home populations cannot necessarily be applied to community-dwelling dementia patients, however, as these individuals tend to be healthier and less functionally impaired than people who are institutionalized. Additionally, dementia patients in the community generally receive care from informal caregivers who are balancing other responsibilities while providing round-the-clock assistance (28). Future studies of community-dwelling dementia patients and their caregivers should be longitudinal, enrolling participants at the earliest possible stages of disease to provide information on patterns of symptoms, caregiver perceptions and treatment patterns over time. Future work should also consider using instruments such and the Neuropsychiatric Inventory (29) to identify the problem behaviors that are most troubling to caregivers and consequently likely to result in psychotropic medication. Interventions could then focus on helping caregivers manage the identified disturbances and the emotional distress that accompanies them. Along similar lines, studies should also examine caregiver reactions to resistance to care, as it has been identified as a predictor of caregiver stress and therefore may be an important risk factor for psychotropic medication (30).

In order for research to move forward, appropriate data sources will need to be developed. Currently, there is a dearth of information available on community-dwelling dementia patients, their medications, and informal caregivers. In fact, one of the largest strengths of this dissertation is the ability to examine caregivers and care recipients

together. We recommend that future efforts focus on gathering detailed dementia patient information in addition to objective and subjective caregiver information, either through the creation of new study cohorts, or through the expansion of existing aging cohorts. These cohorts will be essential for understanding the extent to which psychotropic medications are used in community-dwelling dementia patients and the reasons for their use.

Another recommendation for future research concerns the assessment of risk associated with antipsychotic use in dementia patients. A recent meta-analysis of placebo-controlled trials of antipsychotics in dementia patients released in September 2011 by the Agency for Health Care Research and Quality (AHRQ) found small but statistically significant reductions in problematic behaviors associated with use of aripiprazole, olanzapine, and risperidone (2). These results indicate that despite the risk of significant harm, some dementia patients do benefit from antipsychotic use and that there are subgroups of dementia patients where treatment with antipsychotics may be particularly valuable. Unfortunately, the FDA's antipsychotic black box warning is a blanket warning for all antipsychotics and does not provide information about which antipsychotic poses the greatest risk (31-33). Furthermore, there is little information available regarding risk factors for increased mortality in elderly users of antipsychotics. This lack of information is unacceptable given that there are currently no other treatment options available for managing behavioral disturbances in dementia. We recommend that future research evaluate atypical antipsychotic drugs with respect to their risk of serious cardiovascular events and mortality in elderly dementia patients. We also recommend that research efforts be directed towards finding risk factors that will identify patients at

the greatest risk for a serious adverse event. This detailed risk information is essential for protecting community-dwelling dementia patients, as they are not protected by the federal regulations that guide antipsychotic prescribing in nursing homes.

Finally, building upon the previous suggestions above, we recommend that researchers make a special effort to recruit community-dwelling, minority dementia patients into research on psychotropic medication use. Racial/ethnic minorities are the fastest growing group of dementia patients in the United States (34, 35) and are more likely to remain in the community relative to White/Caucasian patients (23, 36). Additionally, previous research has demonstrated racial/ethnic variation in several variables that may influence psychotropic medication use including dementia knowledge, concerns about dementia, and beliefs about effectiveness of treatment (20). Consequently, a "one size fits all" non-pharmacologic treatment alternative will likely fail at reducing medication use in minority populations. Understanding the predictors of psychotropic medication within diverse groups of community-dwelling patients will be essential for designing culturally-relevant interventions that reduce psychotropic medication among minority dementia patients living in the community.

Racial and ethnic variation in drug response has also been well-described in the literature (37, 38). Although the reasons behind racial heterogeneity of treatment response are not fully understood, they are thought to reflect fundamental differences in the pathogenesis of disease, environment, and distributions of polymorphisms in drug receptors or drug-metabolizing enzymes across racial/ethnic groups (39). Future research of psychotropic medication use in dementia patients should include a diverse group of community-dwelling dementia patients, as race/ethnicity may be a risk factor for adverse

cardiovascular events or death. This information will not only help protect the most vulnerable community-dwelling dementia patients, but will also provide context for observed racial/ethnic disparities in medication use.

5.4 Public Health Policy Implications

The research presented in this dissertation also has important implications for public health policy in terms of demonstrating a need for public health action and recommendations for the type of action that needs to occur. We found that the prevalence of psychotropic medication use among community-dwelling dementia patients was quite high and similar to reports of psychotropic medication use in nursing home residents (4), suggesting that the current health system delivers a largely pharmaceutical based response to managing behavioral disturbances in community-dwelling adults with dementia. This is in direct opposition to the American Academy of Neurology Practice Parameters that support psychotropic intervention only as a second line response after non-pharmaceutical interventions have failed (40). The substantial risks associated with psychotropic medications in combination with the high levels of use in community-dwelling dementia patients are a blatant indication that current health and social systems have failed to provide an appropriate response to dementia care. Based on a review of common dementia treatment practices and our findings of the importance of an informal dementia caregiver in predicting psychotropic medication use, we offer the following practical recommendations for policy changes that will improve dementia care for patients residing in the community.

In the United States, most dementia patient psychotropic medication prescriptions are dispensed by primary care physicians without consultation from a specialist,

geriatrician, gerontological clinical nurse specialist, or nurse practitioner (21). It is therefore reasonable to expect that future efforts at reducing psychotropic medication use in dementia patients will need to include changes to the way general practitioners assess and treat individuals with dementia. At the very least, state medical boards should develop a curriculum for physician education around the management of dementia-related behavioral disturbances and the availability of local social assistance services. This training should be available as continuing medical education.

Although focusing on physician education and physician interactions with patients will address one deficiency of the current health care system and may help eliminate racial/ethnic disparities in medication use, it will likely be insufficient for reducing psychotropic medication use in community-dwelling dementia patients when used in isolation. Our research indicates that perceptions of informal caregivers will also need to be addressed. This point is supported by a 2007 report by Hinton *et al*. that examined the challenges physicians face in managing dementia-related behavioral disturbances. Dementia caregivers often arrive at office visits with intense social and psychological needs that general practitioners are not able to directly address. As a result, doctors may prescribe psychotropics as a way to alleviate caregiver stress associated with managing screaming and hallucinations (41). Although there is evidence that antipsychotics may provide small reductions in dementia-related behavioral disturbances (2), using psychotropic medication as a general strategy to reduce caregiver distress is inappropriate-- nonpharaceutical interventions have been shown to effectively reduce caregiver bother and increase caregiver efficacy (12).

Instead, a comprehensive approach to dementia care that involves both dementia patients and informal caregivers is needed. The focus for dementia treatment needs to be directed away from primary care physicians to a multidisciplinary team including physicians and nurses with special training in gerontology, counselors, social workers, and non-pharmaceutical interventionists. For this type of structural change to occur uniformly across the health care system; however, ambitious, long-term reforms will need to be made to payment systems. Currently, Medicare, the largest insurer for people over 65 years of age, does not offer reimbursements that reflect the time and complexity of care needed by the families and individuals with dementia. As a result, care providers are forced to make difficult decisions regarding patient care in order to balance financial obligations. Changes to the current reimbursement system that recognize the challenges associated with treating dementia are necessary to ensure that providers are able to deliver the most appropriate care to patients and caregivers.

Incentives should also be developed that reward health care organizations for delivering more comprehensive care at early stages of dementia. Health care organizations that do not bear the cost of long-term care or institutionalization have no financial incentive to increase the quality of care early in the disease process, when treatment strategies can be more offensive and less reactionary. Creating a financial incentive to identify patients with dementia and begin early comprehensive treatment will likely play a role in reducing psychotropic medication and also may also reduce costs by delaying institutionalization (41).

The challenges facing informal dementia caregivers and physicians are enormous. The current treatment approach for mood and behavioral disturbances in dementia is

primarily pharmaceutical-based and highlights an opportunity to improve the way the patients with dementia and their informal caregivers are treated. The dementia patient population is growing rapidly so it is imperative that the policies governing the delivery of care in the United States change quickly. Our suggestions for reform include mandatory physician training on the management of dementia-related behavioral disturbances and the availability of local social assistance services, as primary care physicians are usually the first point of contact for dementia patients and their informal caregivers. We also suggest taking the focus away from primary care physicians and directing it toward a multidisciplinary team including physicians and nurses with special training in gerontology, counselors, social workers, and non-pharmaceutical interventionists in order to address the needs to the dementia patient and the informal caregivers. Finally, we recommend increases in health care reimbursements to providers to reflect the complexity of care needed to effectively treat dementia. We also suggest that health care organizations be rewarded for providing comprehensive care as discussed above. Without this change, people with dementia, particularly those exhibiting behavioral symptoms will be unnecessarily exposed to dangerous psychotropic medications.

5.5 Final Comments

Dementia is and will continue to be a significant public health problem. Many patients with dementia are treated unnecessarily with dangerous psychotropic medications. This dissertation expands current knowledge about psychotropic medication use in community-dwelling patients, a large but often over-looked segment of the dementia patient population. Although this work represents only a small step forward

in understanding the relation between caregivers, care recipients, and medication use, we are providing the first evidence that care recipient pain and informal caregiver perceptions influence psychotropic medication use in community-dwelling dementia patients. We also are the first group to identify that predictors of psychotropic medication vary over time and that there are important racial/ethnic disparities in medication use. This dissertation has important implications for the development of interventions aimed at reducing psychotropic medication use in the community and also provides practical directions for future research and policy changes that will improve not only the lives of dementia patients and their caregivers, but other people struggling with chronic disease.

5.6 References

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