

**Caregiving over time:
The impact of the behavioral and psychological symptoms of dementia on caregiver
depression**

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ABSTRACT

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This dissertation was motivated by the growth in the number of elderly with dementia in the United States and worldwide, and the consequent need to assist caregivers who face the chronic stress and consequent negative outcomes of caring for dementia patients for increasingly longer periods of time. While behavioral and psychological symptoms of dementia (BPSD) are routinely cited as important predictors of negative caregiving outcomes, they consist of a wide variety of patient behaviors (e.g., depression, physical aggression and paranoid delusions). This dissertation aimed to further elucidate the BPSD-caregiver relationship by determining if and why individual components of BPSD impacted caregiver depression, how these relationships change over time, and how the timing of behaviors across the disease course affect the caregiver. First, via a systematic literature review we found that despite the significant amount of research conducted examining BPSD and caregiving, the literature focused on the aggregate effect of symptoms rather than on the effect of individual symptoms. Existing studies categorized BPSD based on how they clinically manifest in the patient, rather than from the perspective of how they may differentially impact the caregiver. Second, we tested the differential impact of four symptom clusters derived based on their likely impact on the caregiver (accusatory/aggressive symptoms, non-threatening psychotic symptoms, depressive symptoms, and difficult behaviors) on caregiver depression. All clusters exerted similar effect sizes on caregiver depression, with patient depressive symptoms exerting the strongest and most consistently stable relationship with

caregiver depression. The patient depression-caregiver depression relationship was mediated by both perceived burden to caregivers and impact of symptoms on the patient. Finally, we did not find evidence that the presence of individual BPSD early in the disease course impacted subsequent caregiver depressive symptoms. When examining change patterns over time, we found that most caregivers had stable trajectories of depressive symptoms, with a smaller subset showing more evidence for wear-and-tear over time. Given that there may be a differential effect of individual symptoms on caregivers, research in this field should continue to study the effects of individual BPSD symptoms rather than the cumulative effects of a range of behaviors and should also consider how symptoms may negatively impact caregivers by evoking empathy in addition to increasing burden for the patient. Future work should continue to utilize a longitudinal perspective on caregiving to better characterize the relationship between individual BPSD and caregiver outcomes and to understand varied outcome trajectories. The continued focus on understanding how, why and when BPSD are most detrimental to caregivers can help target and improve patient treatment and caregiver intervention efforts.

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Dedication

This work is dedicated to my family. To my parents—the challenges you have experienced as you have aged have only served to inspire me. To my husband and partner, Philip Noyes—this would never have been possible without your support, love and reassurance. And, of course, the time and freedom you gave me to work. You are amazing and I look forward to aging alongside you. And, of course, to Elijah and his baby sister-to-be, my future caregivers—you are the most wonderful distractions I could possibly have.

Introduction

Increasingly within the United States (U.S.) and globally, informal or family caregivers are relied upon to provide care to a growing number of patients living with dementia.(1;2) Although highly prevalent, caregiving has well-documented negative effects on the health and well-being of caregivers.(3) The caregiving literature suggests that, in general, the cumulative effect of the non-cognitive, or the behavioral and psychological symptoms of dementia (BPSD) are most burdensome to caregivers.(3-10) In order to inform interventions that benefit patients as well as the growing population of caregivers we rely on to care for them, more research is necessary to characterize how, why and when specific groups of BPSD affect caregiver depression. This dissertation aims to address this need.

The growth of dementia in an aging society

By 2030, almost 20% of the U.S. population will be older than 65 years with those older than 85 years becoming the fastest growing segment of the population.(11) With the aging of the population, an increasing number of individuals are living with chronic debilitating diseases that require extensive professional and family care. Dementia, one such chronic illness, is a complex clinical syndrome characterized by a loss of or decline in memory and other cognitive abilities (e.g., ability to recognize or identify objects) severe enough to interfere with daily life.(12) Dementia has many subtypes reflecting different etiologies including: Alzheimer's Disease (AD), Vascular Dementia, Dementia with Lewy Bodies (DLB), Parkinson's Disease, and Frontotemporal Dementia.

By far the most prevalent dementia subtype, AD accounts for 70% of all cases of dementia in elderly Americans.(13) The prevalence of AD among the elderly in the U.S.

is estimated to be 5.1 million, representing 13% of all individuals over age 65.(14) This number is projected to increase by 50% to reach 7.7 million in 2030(15) and up to 16 million in 2050 as the baby boomer generation ages.(16) Among the growing subpopulation of those over age 85, estimates have suggested that up to 50% have AD.(17) AD has no known cure and is currently the 5th leading cause of death in those over age 65 in the U.S.(18) AD is classified by stage: mild to moderate to severe. Early clinical symptoms include difficulty remembering names and recent events; as the disease progresses, the patient has impaired judgment, disorientation, confusion, and trouble speaking, swallowing and walking. In the final stages of AD, the patient is unable to communicate and is completely dependent on others for care. This stage may last a few months or many years.(14)

The behavioral and psychological symptoms of dementia (BPSD)

Although cognitive decline is considered the clinical hallmark of dementia, behavioral symptoms are a common and potentially severe problem complicating dementia. In his original 1906 case report on AD, Alois Alzheimer highlighted paranoid delusions and hallucinations as salient features of the disease.(19) BPSD are often referred to as “problem behaviors” or simply “behavioral disturbances.” BPSD include verbal and physical aggression, agitation, psychotic symptoms (e.g., hallucinations and delusions), sleep disturbances, depression, oppositional behavior, and wandering. In a 1996 consensus statement, BPSD were defined as “signs and symptoms of disturbed perception, thought content, mood, or behavior that frequently occur in patients with dementia.”(20) While the evidence is equivocal, the origin of these behavioral symptoms

is believed to be due to cell atrophy in areas of the brain involved with emotion and behavior. BPSD may also be due to the patient's experience of losing knowledge and understanding of their surroundings, causing fear and frustration that they can no longer express verbally.(21-25)

Although precise estimates vary widely, BPSD are consistently found to be highly prevalent in patients with dementia over the course of their illness.(26-32) In the Cache County population-based studies of patients with dementia, for example, 97% developed one or more symptoms over a five-year period.(33) Beside the substantial impact on the quality of life of people with dementia,(34) BPSD as a whole have been linked to more rapid cognitive and functional decline,(35-39) earlier patient institutionalization,(39-41) increased burden for health care professionals,(42;43) and increased costs of care.(44)

Caregiving for people with dementia

The growth of the elderly population and subsequent increased prevalence of chronic illnesses including dementia results in the need for more patient care. Informal or family caregivers (i.e., unpaid friends or family members who “provide, arrange or oversee needed services because of functional disabilities or health needs”)(45, p.321) frequently provide care to family or other household members affected by dementia. Within the U.S. health care system, there is a heavy reliance on these caregivers although they often have inadequate support, finances, or training for the job.(46-48) Family caregivers are increasingly performing activities which previously would have been provided by government funded health aides or nursing staff.(49) Indeed, caregiving has become a very common role. According to a national population survey,(1) 21% of adults in the

U.S. are caregivers, with one-third caring for more than one patient simultaneously. This percentage will continue to increase as the number of children available to care for older parents continues to decrease.(11)

While positive experiences and outcomes related to caregiving (e.g., improved outlook on life, feeling useful or competent) clearly exist,(50;51) decades of research has uncovered the enormous physiological, psychological and financial costs associated with informal caregiving.(3;52) There is a consensus in the gerontological literature that informal caregivers have increased stress(5-7;53) including family conflicts,(54;55) decreased quality-of-life,(56;57) and increased incidence of depression and anxiety.(5;58) Studies also suggest that caregivers experience more physical illness,(59;60) poorer immune response,(61) and even increased mortality.(62) Because of the growing need to keep caregivers healthy in their challenging roles, a tremendous research initiative has focused on understanding causes of stress in caregivers and developing interventions that can provide long-term support for caregivers.

Caregiving and its consequent stressors occur for family members of patients with a wide range of chronic illnesses including HIV, serious mental illness, and children with disabilities. Yet dementia caregiving has long been the focus of caregiving research due to its pervasiveness, long-term status and well-documented challenges. Research has routinely characterized dementia caregiving as being more stressful than caregiving for other types of illnesses.(63) The increased stressfulness is likely due to the fact that dementia disrupts the lives of patients and their families not only so completely, but also for extended periods of time. Caregivers of people with AD and other dementias provide

more hours of help, on average, than caregivers of other older people, and they serve in their caregiving role for longer periods of time.(1;2) Patients with dementia are also likely to suffer from other medical illnesses including diabetes (20%) and congestive heart failure (25%)(64) resulting in associated excess disability, hospitalizations, and more complicated care regimens. Additionally, the caregivers of dementia patients arguably endure greater emotional challenges in their roles as they must face an ongoing loss in their family member's personality over time culminating in the patient's lack of recognition of the caregiver as well as the patient's eventual death.

The impact of BPSD on caregiver outcomes

Although the literature is inconclusive regarding many risk factors for caregiver distress, researchers have consistently demonstrated associations between BPSD and negative outcomes for caregivers of patients with dementia.(3;5;6;65) These behaviors are reported to be more stressful for caregivers than cognitive and functional problems in the patient.(66-71).

Because of the high prevalence of BPSD and their association with a host of negative patient and caregiver outcomes, public health efforts have focused on developing effective interventions and drug therapies to ameliorate the wide range of BPSD.(72-74) In addition to trying to directly alleviate symptoms in the patient that may be causing distress, a wide variety of caregiving interventions have been developed to help caregivers cope with a range of BPSD. These interventions include: individual and family counseling, support groups, ad hoc counseling, and respite care services.(75-78) Intensive multicomponent interventions that combine several techniques have been

shown to be most effective in reducing institutionalization for patients and burden and depression for dementia caregivers.(76;79) While such interventions are being evaluated, most have not been rigorously tested over long follow-up periods.(76;80) Overall there remains little consensus regarding how to best support caregivers.

Why do BPSD negatively impact caregivers? The role of specific behaviors

Although BPSD are referred to as a singular construct, they actually consist of a wide range of behaviors or symptoms¹ (e.g., wandering, hallucinations, aggression and depression). While researchers and clinicians espouse that BPSD are highly problematic for caregivers, it is less clear which specific symptoms or symptom clusters have the greatest negative impact on the caregiver. For example, in a review of previous studies, Ballard(9) concluded that a wide range of symptoms including withdrawal, apathy, mood, aggression and restlessness are the “most important symptoms” relative to impact on caregivers. The failure to capture the specificity of the unique symptoms is a limitation given that individual symptoms have value in understanding the nature and progression of dementia.(35;36;81)

BPSD symptoms and caregiver distress: A potentially dynamic relationship

As patient-caregiver relationships will only lengthen as new treatments develop to slow the progression of dementia, we must consider how timing and adaptation impact behaviors. The dementia caregiver, in particular, confronts challenges extending

¹ Individual components of BPSD may be referred to as behaviors, symptoms, or symptom clusters.

throughout the disease course, including patient cognitive and functional decline as well as variation in individual BPSD, which are known to change with illness progression.(28;82;83) In general, over the course of dementia, BPSD tend to have a curvilinear pattern of change such that they increase from early to middle stages but decrease in later stages of disease as the patient becomes more impaired with decreased verbal abilities.(84-86) Individual symptoms or symptom clusters, however, appear to exhibit unique courses.(28) In one study, researchers found that as disease progressed and cognition declined, wandering or agitation and physical aggression increased while hallucinations remained stable and delusions declined.(84) Using the same dataset, researchers also found that over time (up to 14 years), disruptive behaviors (sundowning, verbal outbursts, threats, wandering and agitation) increased.(81) Similarly, using population data, there is an overall pattern of increasing symptoms over a 5-year period with variation across individual symptoms.(33)

By studying the impact of timing of behaviors, we may be able to focus on specific stages of the patient-caregiver relationship in which intervention for caregivers would be most beneficial. Furthermore, we must also examine the dynamic relationship between patient behavior and caregiver depression over time. While most caregivers are stable or appear to adapt over time to their stressful role, the impact of specific BPSD on the adaptation process has not been elucidated. Many of the analyses that successfully adopt longitudinal designs to determine potential predictors of caregiver psychosocial adaptation over time (e.g., Aneshensel et al.(65), Gaugler et al.(87)) have not tested the impact of individual symptoms. Establishing how timing of behavior impacts caregiver response relative to individual symptomatology is paramount to understanding the

etiology of caregiver depression and developing effective interventions appropriate to the changing course of disease.

Aims of the Dissertation

The objective of this dissertation is to advance understanding of the relationship between BPSD and caregiving. We systematically examine existing caregiving literature to assess how the relationship between individual BPSD and caregiving outcomes has been studied and propose a new framework for conceptualizing and testing the impact of BPSD on caregivers. Specifically, we propose to categorize BPSD based on how they are likely to impact caregivers, when examining caregiver outcomes. Beyond hypothesizing and testing the differential relationship between individual BPSD and caregiver depression, we consider the role of timing and change over time in these relationships.

We begin, in the first of three papers by examining the existing literature to determine whether individual BPSD have differential impact on caregiver depression by reviewing if and how these relationships have been examined. Next in chapter 2 we build on our findings in chapter 1 by testing the impact of four individual symptom clusters on caregiver depression. The objective is to improve upon previous work by categorizing symptom clusters based on how they impact the caregivers and hypothesizing and testing which individual symptoms may result in worse outcomes for caregivers. Chapter 3 extends beyond chapter 2 findings by addressing the issue of timing relative to the relationship between individual symptoms and caregiver depression. Specifically, we examine whether change in individual symptom clusters impact change in BPSD and test

whether BPSD that occur early in disease course have lasting impact on the development of depression in caregivers.

Together, these three chapters aim to advance the scientific thinking on the relationship between BPSD and caregiver depression. We attempt to close the gaps in current understanding of why BPSD have negative consequences for caregivers by suggesting a new framework for conceptualizing and empirically testing the impact of BPSD. Our work also highlights the issue of timing over the course of the patient-caregiver relationship, a critical perspective on a dyadic relationship extending over increasing time periods.

References

- (1) National Alliance for Caregiving, AARP. Caregiving in the U.S. Washington, DC: AARP; 2004.
- (2) Alzheimer's Association and National Alliance for Caregiving. Families care: Alzheimer's disease caregiving in the United States, 2004. 2004.
- (3) Schulz R, O'Brien AT, Bookwala J, Fleissner K. Psychiatric and physical morbidity effects of dementia caregiving: prevalence, correlates, and causes. *Gerontologist* 1995 Dec;35(6):771-791.
- (4) Black W, Almeida OP. A systematic review of the association between the Behavioral and Psychological Symptoms of Dementia and burden of care. *Int Psychogeriatr* 2004 Sep;16(3):295-315.
- (5) Pinquart M, Sorensen S. Associations of stressors and uplifts of caregiving with caregiver burden and depressive mood: a meta-analysis. *J Gerontol B Psychol Sci Soc Sci* 2003 Mar;58(2):112-128.
- (6) Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. *Gerontologist* 1980 Dec;20(6):649-655.
- (7) Clyburn LD, Stones MJ, Hadjistavropoulos T, Tuokko H. Predicting caregiver burden and depression in Alzheimer's disease. *J Gerontol B Psychol Sci Soc Sci* 2000 Jan;55(1):S2-13.
- (8) Meshefedjian G, McCusker J, Bellavance F, Baumgarten M. Factors associated with symptoms of depression among informal caregivers of demented elders in the community. *The Gerontologist* 1998 Apr;Vol.38(2):247-253.
- (9) Ballard C, Lowery K, Powell I, O'Brien J, James I. Impact of behavioral and psychological symptoms of dementia on caregivers. *International Psychogeriatrics* 2000;Vol.12(Suppl1):93-105.
- (10) Donaldson C, TARRIER N, Burns A. The impact of the symptoms of dementia on caregivers. *Br J Psychiatry* 1997 Jan;170:62-68.
- (11) He W, Sengupta M, Velkoff V, DeBarros K. 65+ in the United States: 2005. Bethesda, MD: Commerce Dept., Economics and Statistics Administration, Census Bureau, and Health and Human Services Dept., National Institutes of Health, National Institute on Aging; 2005.
- (12) Weiner MF, Lipton A. The Dementias : diagnosis and management, 3rd ed. Washington, DC: American Psychiatric Publishing, 2003.

- (13) Plassman BL, Langa KM, Fisher GG, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology* 2007;29(1-2):125-132.
- (14) 2009 Alzheimer's disease facts and figures. *Alzheimers Dement* 2009 May;5(3):234-270.
- (15) Herbert L, Scherr P, Evans DA. Projections of the Prevalence and Incidence of Dementias using the 2000 Census. *Arch Neurol* 2003;60:1119-1122.
- (16) Sloane PD, Zimmerman S, Suchindran C, et al. The public health impact of Alzheimer's disease, 2000-2050: potential implication of treatment advances. *Annu Rev Public Health* 2002;23:213-231.
- (17) Evans DA. Estimated prevalence of Alzheimer's disease in the United States. *Milbank Q* 1990;68(2):267-289.
- (18) Heron MP, Smith BL. Deaths: leading causes for 2003. *Natl Vital Stat Rep* 2007 Mar 15;55(10):1-92.
- (19) About a peculiar disease of the cerebral cortex. By Alois Alzheimer, 1907 (Translated by L. Jarvik and H. Greenson). *Alzheimer Dis Assoc Disord* 1987;1(1):3-8.
- (20) Finkel SI, Costa e Silva, Cohen G, Miller S, Sartorius N. Behavioral and psychological signs and symptoms of dementia: a consensus statement on current knowledge and implications for research and treatment. *Int Psychogeriatr* 1996;8 Suppl 3:497-500.
- (21) Burns A, Jacoby R, Levy R. Psychiatric phenomena in Alzheimer's disease. I: Disorders of thought content. *Br J Psychiatry* 1990 Jul;157:72-74.
- (22) Burns A, Jacoby R, Levy R. Psychiatric phenomena in Alzheimer's disease. II: Disorders of perception. *Br J Psychiatry* 1990 Jul;157:76-4.
- (23) Burns A, Jacoby R, Levy R. Psychiatric phenomena in Alzheimer's disease. III: Disorders of mood. *Br J Psychiatry* 1990 Jul;157:81-84.
- (24) Burns A, Jacoby R, Levy R. Psychiatric phenomena in Alzheimer's disease. IV: Disorders of behaviour. *Br J Psychiatry* 1990 Jul;157:86-94.
- (25) Burns A. Behavioral and psychological symptoms of dementia and caregiver burden. *Int Psychogeriatr* 2000;12(Suppl 1):347-350.
- (26) Steinberg M, Lyketsos CG. Psychiatric disorders in people with dementia. In Weiner, Myron F (Ed); Lipton, Anne M (Ed). *The American Psychiatric Publishing textbook of Alzheimer disease and other dementias*. (pp. 263-281). Arlington, VA, US: American Psychiatric Publishing, Inc. 2009.

- (27) Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *JAMA* 2002 Sep 25;288(12):1475-1483.
- (28) Aalten P, de Vugt ME, Jaspers N, Jolles J, Verhey FR. The course of neuropsychiatric symptoms in dementia. Part I: findings from the two-year longitudinal Maasbed study. *Int J Geriatr Psychiatry* 2005 Jun;20(6):523-530.
- (29) Torti FM, Jr., Gwyther LP, Reed SD, Friedman JY, Schulman KA. A multinational review of recent trends and reports in dementia caregiver burden. *Alzheimer Dis Assoc Disord* 2004 Apr;18(2):99-109.
- (30) Sink KM, Covinsky KE, Newcomer R, Yaffe K. Ethnic differences in the prevalence and pattern of dementia-related behaviors. *J Am Geriatr Soc* 2004 Aug;52(8):1277-1283.
- (31) Steinberg M, Sheppard JM, Tschanz JT, et al. The incidence of mental and behavioral disturbances in dementia: the Cache County study. *J Neuropsychiatry Clin Neurosci* 2003;15(3):340-345.
- (32) Tariot PN, Mack JL, Patterson MB, et al. The Behavior Rating Scale for Dementia of the Consortium to Establish a Registry for Alzheimer's Disease. The Behavioral Pathology Committee of the Consortium to Establish a Registry for Alzheimer's Disease. *Am J Psychiatry* 1995 Sep;152(9):1349-1357.
- (33) Steinberg M, Shao H, Zandi P, et al. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. *Int J Geriatr Psychiatry* 2008 Feb;23(2):170-177.
- (34) Banerjee S, Smith SC, Lamping DL, et al. Quality of life in dementia: more than just cognition. An analysis of associations with quality of life in dementia. *J Neurol Neurosurg Psychiatry* 2006 Feb;77(2):146-148.
- (35) Chui HC, Lyness SA, Sobel E, Schneider LS. Extrapyrarnidal signs and psychiatric symptoms predict faster cognitive decline in Alzheimer's disease. *Arch Neurol* 1994; 51:676-681. *Arch Neurol* 1994;51:676-681.
- (36) Scarmeas N, Brandt J, Albert M, et al. Delusions and hallucinations are associated with worse outcome in Alzheimer disease. *Arch Neurol* 2005 Oct;62(10):1601-1608.
- (37) Ropacki SA, Jeste DV. Epidemiology of and risk factors for psychosis of Alzheimer's disease: a review of 55 studies published from 1990 to 2003. *Am J Psychiatry* 2005 Nov;162(11):2022-2030.

- (38) Lopez OL, Wisniewski SR, Becker JT, Boller F, DeKosky ST. Psychiatric medication and abnormal behavior as predictors of progression in probable Alzheimer disease. *Arch Neurol* 1999 Oct;56(10):1266-1272.
- (39) Magni E, Binetti G, Bianchetti A, Trabucchi M. Risk of mortality and institutionalization in demented patients with delusions. *J Geriatr Psychiatry Neurol* 1996 Jul;9(3):123-126.
- (40) Cohen CA, Gold DP, Shulman KI, Wortley JT, McDonald G, Wargon M. Factors determining the decision to institutionalize dementing individuals: a prospective study. *Gerontologist* 1993 Dec;33(6):714-720.
- (41) Steele C, Rovner B, Chase GA, Folstein M. Psychiatric symptoms and nursing home placement of patients with Alzheimer's disease. *Am J Psychiatry* 1990 Aug;147(8):1049-1051.
- (42) Aneshensel CS, Botticello AL, Yamamoto-Mitani N. When caregiving ends: the course of depressive symptoms after bereavement. *J Health Soc Behav* 2004 Dec;45(4):422-440.
- (43) Sourial R, McCusker J, Cole M, Abrahamowicz M. Agitation in demented patients in an acute care hospital: prevalence, disruptiveness, and staff burden. *Int Psychogeriatr* 2001 Jun;13(2):183-197.
- (44) Herrmann N, Lanctot KL, Sambrook R, et al. The contribution of neuropsychiatric symptoms to the cost of dementia care. *Int J Geriatr Psychiatry* 2006 Oct;21(10):972-976.
- (45) Gaugler JE, Kane RA, Langlois J. Assessment of family caregivers of older adults. In: Kane RL, Kane RA, eds. *Assessing Older Persons: Measures, Meaning and Practical Applications*. New York: Oxford University Press, 2003:320-359.
- (46) Langa KM, Chernew ME, Kabeto MU, et al. National estimates of the quantity and cost of informal caregiving for the elderly with dementia. *J Gen Intern Med* 2001 Nov;16(11):770-778.
- (47) Levine C. The loneliness of the long-term care giver. *N Engl J Med* 1999 May 20;340(20):1587-1590.
- (48) Canam C, Acorn S. Quality of life for family caregivers of people with chronic health problems. *Rehabil Nurs* 1999 Sep;24(5):192-6, 200.
- (49) Hoffmann RL, Mitchell AM. Caregiver burden: historical development. *Nurs Forum* 1998 Oct;33(4):5-11.
- (50) Cohen CA, Colantonio A, Vernich L. Positive aspects of caregiving: rounding out the caregiver experience. *Int J Geriatr Psychiatry* 2002 Feb;17(2):184-188.

- (51) Tarlow B. Positive Aspects of Caregiving. *Research on Aging* 2004;26(4):429-453.
- (52) Pinquart M, Sorensen S. Differences between caregivers and noncaregivers in psychological health and physical health: a meta-analysis. *Psychol Aging* 2003 Jun;18(2):250-267.
- (53) Cannuscio CC, Jones C, Kawachi I, Colditz GA, Berkman L, Rimm E. Reverberations of family illness: a longitudinal assessment of informal caregiving and mental health status in the Nurses' Health Study. *Am J Public Health* 2002 Aug;92(8):1305-1311.
- (54) Cameron JI, Franche RL, Cheung AM, Stewart DE. Lifestyle interference and emotional distress in family caregivers of advanced cancer patients. *Cancer* 2002 Jan 15;94(2):521-527.
- (55) Narayan S, Lewis M, Tornatore J, Hepburn K, Corcoran-Perry S. Subjective responses to caregiving for a spouse with dementia. *J Gerontol Nurs* 2001 Mar;27(3):19-28.
- (56) Argimon JM, Limon E, Vila J, Cabezas C. Health-related quality of life in carers of patients with dementia. *Fam Pract* 2004 Aug;21(4):454-457.
- (57) Rees J, O'Boyle C, MacDonagh R. Quality of life: impact of chronic illness on the partner. *J R Soc Med* 2001 Nov;94(11):563-566.
- (58) Cuijpers P. Depressive disorders in caregivers of dementia patients: a systematic review. *Aging Ment Health* 2005 Jul;9(4):325-330.
- (59) Mausbach BT, Patterson TL, Rabinowitz YG, Grant I, Schulz R. Depression and distress predict time to cardiovascular disease in dementia caregivers. *Health Psychol* 2007 Sep;26(5):539-544.
- (60) Vitaliano PP, Zhang J, Scanlan JM. Is caregiving hazardous to one's physical health? A meta-analysis. *Psychol Bull* 2003 Nov;129(6):946-972.
- (61) Kiecolt-Glaser JK, Glaser R, Gravenstein S, Malarkey WB, Sheridan J. Chronic stress alters the immune response to influenza virus vaccine in older adults. *Proc Natl Acad Sci U S A* 1996 Apr 2;93(7):3043-3047.
- (62) Schulz R, Beach SR. Caregiving as a risk factor for mortality: the Caregiver Health Effects Study. *JAMA* 1999 Dec 15;282(23):2215-2219.
- (63) Ory MG, Hoffman RR, III, Yee JL, Tennstedt S, Schulz R. Prevalence and impact of caregiving: a detailed comparison between dementia and nondementia caregivers. *Gerontologist* 1999 Apr;39(2):177-185.

- (64) Newcomer RJ, Fox PJ, Harrington CA. Health and long-term care for people with Alzheimer's disease and related dementias: policy research issues. *Aging Ment Health* 2001 May;5 Suppl 1:S124-S137.
- (65) Aneshensel CS, Pearlin LI, Mullan J.T., Zarit SH, Whitlach C.J. Profiles in caregiving: The unexpected career. San Diego: Academic Press, 1995.
- (66) Allegri RF, Sarasola D, Serrano CM, et al. Neuropsychiatric symptoms as a predictor of caregiver burden in Alzheimer's disease. *Neuropsychiatr Dis Treat* 2006 Mar;2(1):105-110.
- (67) Donaldson C, Tarrier N, Burns A. Determinants of carer stress in Alzheimer's disease. *International Journal of Geriatric Psychiatry* 1998 Apr;Vol.13(4):248-256.
- (68) Croog SH, Burleson JA, Sudilovsky A, Baume RM. Spouse caregivers of Alzheimer patients: problem responses to caregiver burden. *Aging Ment Health* 2006 Mar;10(2):87-100.
- (69) Hooker K, Bowman SR, Coehlo DP, et al. Behavioral change in persons with dementia: relationships with mental and physical health of caregivers. *J Gerontol B Psychol Sci Soc Sci* 2002 Sep;57(5):453-460.
- (70) de Vugt ME, Stevens F, Aalten P, et al. Behavioural disturbances in dementia patients and quality of the marital relationship. *Int J Geriatr Psychiatry* 2003 Feb;18(2):149-154.
- (71) Haley WE, Brown SL, Levine EG. Family Caregivers Appraisals of Patient Behavioral Disturbance in Senile Dementia. *Clinical Gerontologist* 1987;6(4):25-34.
- (72) Hinchliffe A, Hyman I, Blizard B, Livingston G. Behavioural complications of dementia: Can they be treated? *Int J Geriatr Psychiatry* 1995;10(10):839-847.
- (73) Tariot PN, Schneider LS, Katz IR. Anticonvulsant and other non-neuroleptic treatment of agitation in dementia. *J Geriatr Psychiatry Neurol* 1995 Oct;8 Suppl 1:S28-S39.
- (74) Lyketsos CG. Neuropsychiatric symptoms (behavioral and psychological symptoms of dementia) and the development of dementia treatments. *Int Psychogeriatr* 2007 Jun;19(3):409-420.
- (75) Coon DW, Evans B. Empirically based treatments for family caregiver distress: what works and where do we go from here? *Geriatr Nurs* 2009 Nov;30(6):426-436.

- (76) Pinquart M, Sorensen S. Helping caregivers of persons with dementia: which interventions work and how large are their effects? *Int Psychogeriatr* 2006 Dec;18(4):577-595.
- (77) Tremont G, Davis JD, Bishop DS, Fortinsky RH. Telephone-delivered psychosocial intervention reduces burden in dementia caregivers. *Dementia: The International Journal of Social Research and Practice* 2008 Nov;Vol.7(4):503-520.
- (78) Schulz R, O'Brien A, Czaja S, et al. Dementia caregiver intervention research: in search of clinical significance. *Gerontologist* 2002 Oct;42(5):589-602.
- (79) Mittelman MS, Brodaty H, Wallen AS, Burns A. A three-country randomized controlled trial of a psychosocial intervention for caregivers combined with pharmacological treatment for patients with Alzheimer disease: effects on caregiver depression. *Am J Geriatr Psychiatry* 2008 Nov;16(11):893-904.
- (80) Mittelman MS. Psychosocial intervention research: challenges, strategies and measurement issues. *Aging Ment Health* 2008 Jan;12(1):1-4.
- (81) Scarmeas N, Brandt J, Blacker D, et al. Disruptive behavior as a predictor in Alzheimer disease. *Arch Neurol* 2007 Dec;64(12):1755-1761.
- (82) Davis LL, Buckwalter K, Burgio LD. Measuring problem behaviors in dementia: developing a methodological agenda. *ANS Adv Nurs Sci* 1997 Sep;20(1):40-55.
- (83) Aalten P, de Vugt ME, Jaspers N, Jolles J, Verhey FR. The course of neuropsychiatric symptoms in dementia. Part II: relationships among behavioural sub-syndromes and the influence of clinical variables. *Int J Geriatr Psychiatry* 2005 Jun;20(6):531-536.
- (84) Holtzer R, Tang MX, Devanand DP, et al. Psychopathological features in Alzheimer's disease: course and relationship with cognitive status. *J Am Geriatr Soc* 2003 Jul;51(7):953-960.
- (85) Devanand DP. Use of the Columbia University Scale to assess psychopathology in Alzheimer's disease. *Int Psychogeriatr* 1997;9 Suppl 1:137-142.
- (86) Mittelman MS, Roth DL, Haley WE, Zarit SH. Effects of a caregiver intervention on negative caregiver appraisals of behavior problems in patients with Alzheimer's disease: results of a randomized trial. *J Gerontol B Psychol Sci Soc Sci* 2004 Jan;59(1):27-34.
- (87) Gaugler JE, Kane RL, Kane RA, Newcomer R. The longitudinal effects of early behavior problems in the dementia caregiving career. *Psychol Aging* 2005 Mar;20(1):100-116.

Chapter 1:

The problem with “problem behaviors”: A systematic review of the association between individual patient behavioral and psychological symptoms and caregiver depression and burden within the dementia patient-caregiver dyad

Abstract

Within the caregiving literature, behavioral and psychological symptoms of dementia (BPSD) are routinely cited as important predictors of negative caregiving outcomes including caregiver burden, caregiver depression, and nursing home placement. Although BPSD consist of a wide variety of patient behaviors including depression, physical aggression and paranoid delusions, they are routinely grouped together as one construct to differentiate them from cognitive symptoms of dementia. Individual behaviors may operate through distinct causal mechanisms, ultimately having differential impact on caregiver outcomes. Determining the specific BPSD behaviors that result in negative mental health for caregivers can help elucidate the stress process for caregivers and facilitate the development of effective interventions for dementia caregivers. Our aim was to determine whether existing studies have tested the differential impact of individual symptoms or symptom clusters as well as the reasons why one symptom type differentially impacts caregiver outcomes. We conducted a systematic review of the scientific literature to: (1) determine how and why individual BPSD were categorized; (2) determine which symptoms or clusters of symptoms exert negative impact on caregivers; (3) identify causal mechanisms studied; and (4) identify gaps in the literature regarding how timing affects these relationships. Based on a review of English-language papers cited in the PUBMED and PsychINFO databases from 1990-2010, we identified 35 original research articles that examined the impact of an individual behavior symptom relative to caregiver burden or depression/depressive symptoms. The studies had no consistent system for categorizing symptoms and made use of 25 different assessment methods of BPSD. Although depression, aggression and sleep disturbances were the most frequently identified patient symptoms to impact caregiver outcomes, a wide range of symptoms were reported as being impactful for

caregivers, and the evidence is not conclusive as to whether some symptoms are more important than others and vary in their impact over time. The studies reviewed were largely exploratory relative to the differential impact of individual BPSD and did not focus on testing causal mechanisms by which specific symptoms would exert more impact on caregiver mental health than others. Overall, the research examining BPSD and caregiver outcomes aggregates a range of symptoms as BPSD or else categorizes them based on how they manifest in the patient, failing to capture, perhaps the appropriate construct for caregiver interventions. Future research may benefit from the re-conceptualization of BPSD from the perspective of their impact on the caregiver to examine hypothesis-driven differences among BPSD symptom clusters. Additionally, further investigation of the impact of timing as well as the role of dementia illness stage, and dementia subtype diagnosis on the patient behavior and caregiver outcome relationship is warranted.

Introduction

Increasingly within the United States (U.S.) and globally, informal or family caregivers, i.e., unpaid friends or family members who “provide, arrange or oversee needed services because of functional disabilities or health needs,” (1, p.321) are relied upon to provide care to a growing number of patients living with dementia. While family caregiving has become a very common role (according to a national population survey, 21% of adults in the US are caregivers),(2) it has negative effects on the health and well-being of caregivers.(3) Dementia caregiving, in particular, has been the focus of caregiving research due to its pervasiveness, long-term status and well-documented challenges. In 2008, almost 10 million family members, friends, and neighbors provided an estimated 8.5 billion hours of unpaid care for a person with AD or other dementias.(4)

Although the caregiving literature is inconclusive regarding many risk factors for dementia caregiver distress, researchers have consistently demonstrated associations between the non-cognitive, or the behavioral and psychological symptoms of dementia (BPSD) and negative outcomes for caregivers of patients with dementia.(3;5-11) BPSD are often referred to as “problem behaviors” or simply “behavioral disturbances” and include verbal and physical aggression, agitation, psychotic symptoms (e.g., hallucinations and delusions), sleep disturbances, depression, oppositional behavior, and wandering. These behaviors are reported to be more stressful for caregivers than cognitive and functional problems in the patient,(12-17) perhaps due to the capricious nature of BPSD. While the functional and cognitive trajectory for the dementia patient follow an expected steady decline, behavior problems can ebb and flow, which can leave the caregiver less prepared to handle the behaviors adequately. Additionally, because they effectively alter the patient’s personality, these behaviors may serve as more

dramatic reminders of the major changes that have occurred in the patient and the loss experienced by the caregiver. BPSD are also associated with more caregiver anger-resentment toward the patient than other aspects of the disease (e.g., cognitive decline),(14) suggesting that there is an emotional response to BPSD which could negatively impact caregiver health outcomes.

While BPSD consist of a wide range of patient behaviors, in caregiving research they are most often measured cumulatively as one construct to be differentiated from the cognitive symptoms of dementia. The vast majority of routinely cited references published in the past 20 years as evidence for the relationship between BPSD and caregiver negative outcomes (n=23), (3;5;6;8;9;11;18-34) did not examine or even review the effect of individual symptoms (e.g., delusions) or separate clusters of symptoms (e.g., psychotic behaviors).²

Moving forward, we believe that individual aspects of BPSD should be examined to determine whether there are specific components of the objective stress of BPSD that result in differential outcomes for caregivers. While aggregated BPSD measures may have increased reliability over single item measures, the failure to capture the complexity of unique behaviors limits our understanding of whether there are particular aspects of dementia behavior which have more deleterious effects for caregivers, especially given that individual symptoms clearly have value in understanding the nature and progression of dementia. (Hallucinations and delusions, for example, appear to be associated with more rapid patient cognitive and functional

² Only two review articles noted the importance of examining individual symptoms (21;35) and of the two original research articles that examined individual patient symptoms and caregiver outcomes, one (25) examined only a limited range of symptoms and the other included a cumulative measure of BPSD in the final multivariate model (24).

decline.(36;37) Behaviors such as sundowning, however, have only been associated with faster cognitive decline.(38))

Certain individual patient symptoms or symptom clusters may have greater negative mental health consequences for the caregiver than others because they may be more difficult to manage physically, may be taken more personally by the caregiver, or may serve as more dramatic reminders of loss of a loved one. Specific psychotic behaviors (e.g., delusions of abandonment, paranoid delusions) may be particularly disturbing to caregivers who are being accused of not helping the patient despite all their efforts, whereas other psychotic behaviors that do not involve the caregiver (e.g., auditory hallucinations) may be less threatening to the caregiver, therefore resulting in less negative consequences for the caregiver. Individual behaviors may ultimately affect the caregiver's mood and ability to effectively care for the patient via different pathways, i.e., by differentially evoking more burden, fear, or sympathy. Understanding whether specific BPSD have more negative impact on caregivers as well as the mechanism by which this occurs, can help to more effectively target treatment and intervention efforts for patient-caregiver dyads.

Furthermore, as patient-caregiver relationships will only lengthen as new treatments develop to slow the progression of dementia, we have to consider the role of timing of and adaptation to behaviors. The dementia caregiver confronts challenges extending throughout the disease course, including patient cognitive and functional decline as well as variation in individual BPSD, which are known to change with illness progression.(39-41) Establishing whether and how timing of behavior impacts caregiver response relative to individual symptomatology is paramount to understanding the etiology of caregiver depression and developing effective interventions appropriate to the changing course of disease. By studying the impact of timing of

behaviors, we may, for example, be able to focus on specific stages of the patient-caregiver relationship in which intervention for caregivers would be most beneficial.

Our aim was to review literature on the relationship between BPSD and caregiver outcomes to determine whether there are known symptoms or symptom clusters which exert undue negative impact on caregivers. Additionally, we review systems used for classifying BPSD symptom clusters and determine whether there have been any mechanisms studied by which individual BPSD symptoms negatively affect caregivers. Finally, we look to see how the role of timing of symptoms has been examined within the literature.

Methods

Materials for this review were primarily identified through searches of two electronic databases for peer-reviewed published papers: the MEDLINE/Pubmed and PsychInfo. Search terms were selected based on initial review of relevant keywords across databases that were likely to yield relevant results. Initial search terms included the following keywords and/or subject headings: (1) “dementia” or “Alzheimer” and (2) “caregivers” or “caregiving” and (3) “behavior symptom” or “BPSD” or “psychiatric” or “neuropsychiatric” or “hallucination” or “delusion” or “aggression” or “agitation” or “wandering” or “psychosis” or “depression” or “behavior.” This search yielded a total of 543 unique papers. A search of related articles in these databases, references in review papers and other relevant papers, and consultation with recognized experts yielded an additional 85 papers for review.

An initial set of 628 papers was reviewed. Inclusion criteria were as follows: (1) published in the last 20 years (i.e., after 1989, in order to focus the review on the most recent information regarding caregiving); (2) written in English; (3) peer-reviewed; (4) original research (i.e., no

review articles); (5) participants were informal or family caregivers of older adults with Alzheimer's disease or dementia in general; (6) included measure of caregiver depression, depressive symptoms or caregiver burden as an outcome;³ and (7) included as exposure variable at least one specific dementia patient behavioral or psychological symptom/symptom cluster. Studies were included even if patient behavior-caregiver outcomes were not the primary research interest. Articles were excluded if they were (1) case reports, cases series or contained 20 or fewer subjects; (2) assessed BPSD as a cumulative variable; (3) focused on a specific subtype of dementia other than Alzheimer's disease; or (4) did not perform a test to determine whether the association between individual patient behaviors and caregiver outcomes was statistically significant (e.g., baseline data from clinical trials that reported mean scores of caregiver distress outcomes for two or more symptoms).⁴

The final number of papers included was 35. Ninety-four percent of studies examined were excluded mainly because they were: intervention studies designed to examine change in caregiver distress, validation studies of BPSD instruments or did not study specific symptoms as opposed to BPSD as a single exposure variable.

Final studies included in the analysis were reviewed to: (1) determine reasons for testing individual BPSD or utilizing specific classification systems; (2) determine which individual

³ Studies that examine the impact of BPSD on caregiver outcomes explore a wide range of caregiver outcomes from depression to marital quality to institutionalization. Because of the paucity of studies examining individual symptoms relative to caregiver outcomes, we included studies that used caregiver depression or caregiver burden as outcomes in this review. We chose not to include outcomes such as institutionalization in our analysis which may be more indirect measures of caregiver distress as they are likely influenced by outside factors such as finances, insurance, and other comorbidities that require skilled nursing care.

⁴ We separately reviewed these 'descriptive-only studies' (n=17) due to the lack of studies meeting full inclusion and exclusion criteria, and they are briefly discussed in the results section.

symptoms or clusters were tested and had impact on caregiver outcomes; (3) identify any causal mechanisms hypothesized and tested; and (4) determine if and how the role of timing of symptoms was studied. As part of this analysis we abstracted the following study data: design, setting, population, diagnosis, exposure and outcome measures, BPSD categorization schemas, analytical approaches, and control for potential confounding.

Impactful symptoms/symptom clusters were operationalized as follows: symptoms with effect estimates designated as statistically significant in adjusted analyses (or unadjusted when not available) based on p-value $<.05$ or with 95% confidence intervals that did not include null values. In our review of findings across studies, we retained all original categorizations of symptoms by investigators and only combined symptoms when they represented the same construct but had different labels (e.g., depression and dysphoria were combined into one category referred to as depression). Symptoms that were combined by authors but consisted of more than one construct were separated when appropriate (e.g., we separated aggression/agitation, a single category within the Neuropsychiatric Inventory,(42) into two symptoms, namely, aggression and agitation). (See Appendix 1.A for complete list of modifications to original categorization schemas.) We also excluded memory problems as a type of BPSD as the focus of this paper is on non-cognitive behavioral and psychological symptoms. We tallied which symptoms were reported as impactful across relevant studies and also examined how often symptoms were reported as impactful relative to how often the symptom was examined. All articles were examined to determine whether there were a priori hypotheses regarding which symptoms would have more severe effects for caregivers. Additionally, we noted whether studies included mediation analyses to determine causal mechanisms for patient-

caregiver associations. Finally, we reviewed study designs in detail to assess the role of timing of symptoms within longitudinal designs.

When analyzing the results, in addition to examining findings across all studies, we initially examined studies that assessed caregiver burden (n=23) and caregiver depression or depressive symptoms (n=17) separately because caregiver burden and depression are different constructs. Five studies examined both caregiver burden and caregiver depression as outcomes.(13;43-46) These outcomes were considered separately, for a total of 35 papers and 40 outcomes assessed. Information from each study was extracted and are presented in Tables 1.1 and 1.2 (Table 1.1: n=17, Table 1.2: n=23). These data are organized according to study author and list all symptoms tested and whether each impacted the outcome of interest. Finally, we reviewed differences in study population and overall study quality to determine potential sources of heterogeneous findings.

Results

Approaches to measuring and categorizing individual symptoms

Across the 35 studies that met criteria and investigated at least one individual symptom or symptom cluster, 25 different scales were used to measure different aspects of BPSD. Ten (29%) reviewed studies(12;43;44;47-53) made use of one of the following commonly-used scales to study a broad range of behaviors: (1) the Behavioral Pathology in Alzheimer's disease (BEHAVE-AD) rating scale(54) which assesses behavior occurrence over seven domains: delusions, hallucinations, activity disturbances, aggression, sleep, affective symptoms, and anxiety and (2) the Neuropsychiatric Inventory (NPI)(42) which assesses ten individual behaviors (delusions, hallucinations, agitation/ aggression, disinhibition, aberrant motor

behavior, irritability, dysphoria, anxiety, apathy, and euphoria) with follow-up questions on severity and frequency of behavior. Measures vary as to whether they assess and/or give weight to the frequency of behavior occurrence (e.g., in the Revised Memory and Behavior Problems Checklist(55) the caregiver notes how often behavior occurred on a five-point Likert scale). Other studies employed one or more assessments used to measure more specific aspects of symptomatology: for example, four studies(53;56-58) used a version of the Geriatric Depression Scale (GDS)(59) which measures patient depression using either 15 or 30 dichotomous (yes/no) questions and one study(43) employed the Cohen-Mansfield Agitation Inventory,(60) a 36-item assessment designed to measure agitation symptoms in dementia patients including spitting, fidgety behavior, and sexual aggressiveness. Additionally, not all studies made use of validated BPSD scales, instead relying on clinical diagnoses of behaviors such as psychosis(61) or original lists of individual items to measure BPSD.(62;63)

There was no consistent approach to the categorization of symptoms across studies. Two studies did not provide any information on categorization schema(25;58) and almost half (n=17)(12;47;48;50;52;61-71) did not employ any system of categorization, instead using select individual items or diagnoses. The remainder of studies either used (1) subscales of instruments (e.g., Robinson et al(72) used existing subscales of the 24-item Revised Memory and Behavior Problems Checklist (RMBC)(55) to examine depression and disruptive behaviors) or (2) subscales and select individual scale items (e.g., Donaldson et al(13) examined overall patient depression, psychotic behaviors, and behavioral disturbance as well as specific items such as hallucinations). The use of subscales and/or individual items resulted in the testing of a range of symptoms/symptom clusters that often include overlapping constructs: for example, while some studies(13;61) use the broader category of “psychosis,” others delineated between specific

psychotic behaviors such as experiencing hallucinations or delusions (e.g., Allegri et al.(12), Shaji et al.(50)). Finally, seven studies (20%) employed factor analytic techniques to categorize symptoms based on how they clustered within patients.(14;46;51;53;57;73;74)

Symptoms that impact caregiver outcomes

No symptom/symptom cluster was consistently identified as having negative impact on either caregiver burden or caregiver depression by the majority of studies examined. For those studies assessing caregiver depression (see Table 1.3), 19 different patient symptoms/symptom clusters were cited as significantly impacting caregivers. Patient depression was the most frequently reported symptom associated with caregiver depression(13;45;52;61;65;66) (35%) although sleep disturbances(13;44;45) (18%), anger/aggression(25;75) (12%), psychosis (13;61) (12%) and agitation (43;73) (12%) were also reported by multiple studies.

Twenty-eight different symptoms/symptom clusters were cited as impactful for caregiver burden (see Table 1.3). Anger/aggression(43;44;46;47;50;71) (26%) and depression(13;45;48;62) (17%) were the most frequently cited patient symptoms having impact on caregiver burden although sleep disturbances(12;45;69) (13%) and repetitive behavior(43;56;63) (13%) were also reported by multiple studies.

We ultimately included caregiver burden and depression studies together for analyses after finding no substantial differences between them. Combining the caregiver burden and depression studies (n=35 articles that assessed n=40 outcomes), we identified 36 different symptoms which had negative impact on caregivers. Only one study(64) did not find any specific behavior pattern to be stressful. The most commonly reported symptoms for either caregiver burden or depression were: depression(13;45;48;52;57;62;65;66;73) (25%),

anger/aggression(25;43;44;46;47;50;71;75) (20%), and sleep disturbances(12;13;44;45;69) (15%). Other symptoms reported as impactful by at least three studies were paranoia,(45;51;69) repetitive behavior,(43;56;63) anxiety,(12;44;51) activity disturbances,(44;50;51) and disruptive behavior.(58;72;76)

Because only those symptoms tested as predictors have the potential to have demonstrated impact on caregiver outcomes, we examined how often specific symptoms/symptom clusters were tested within studies. The following 13 symptoms were examined by at least three individual papers: affective symptoms, agitation, anger/aggression, activity disturbances, anxiety, delusions, depression, disinhibition/acting out, disruptive behaviors, hallucinations, paranoia, repetitive behavior, and sleep disturbances. The most commonly cited impactful symptoms were also those most frequently tested: 66% of reviewed studies tested the impact of depression, 43% tested the impact of anger/aggression, and 34% tested the impact of sleep disturbances. On the other hand, symptoms less frequently cited as having an impact, e.g., anxiety and paranoia, were each tested by only 9% of reviewed papers.

Limiting analyses to the 13 most commonly tested symptoms, we assessed the proportion of studies finding a symptom to be impactful using the number of studies in which the symptom was examined as the denominator.⁵ Six symptoms impacted caregivers in at least 75% of the studies in which they were examined: anxiety, paranoia, activity disturbances, disruptive behaviors, agitation and repetitive behavior. Among the three most commonly reported impactful symptoms, we found that patient depression impacted caregivers in 40% of the studies,

⁵ Because five articles examined multiple outcomes (caregiver burden and caregiver depression), each outcomes assessed is counted as a separate study for the purpose of this analysis resulting in each symptom having the potential to be examined over n=40 cases.

anger/aggression impacted caregivers in 50% of the studies, and sleep disturbances impacted caregivers in 43% of studies. On the other hand, while the effect of patient hallucinations was examined in six studies, only one found the symptom to affect caregiver burden(13); similarly, while delusions were tested seven times, in only two cases were they found to have negative impact on caregiver outcomes(49;50).

As noted previously, there were 17 studies(55;77-85;85-92) excluded from this systematic review because they did not use statistical analyses to discern which symptoms resulted in more negative caregiver outcomes. Similar to the 35 studies included in our review, these studies also suggest that a wide range of symptoms may have negative impact on caregivers' level of burden or depression. Among these studies, 71% (n=12) reported that patient aggression, sleep disturbances or depression had negative impact on caregivers. Agitation, however, was the most frequently reported symptom (26%). We further reviewed papers(16;93) that examined the impact of individual symptoms on negative outcomes other than burden and depression with similarly heterogeneous findings.

Causal mechanisms by which individual BPSD impact caregivers

None of the studies tested causal mechanisms by which a specific symptom/symptom cluster resulted in caregiver depression or burden. Furthermore, none of the studies presented a priori hypotheses indicating one symptom would specifically result in increased caregiver depression or burden than other symptoms. The overwhelming majority of studies were either exploratory in nature (i.e., interested in assessing which symptoms had impact on caregivers) or tested hypotheses about other issues within the caregiving relationship such as the role of gender(56), attachment style(48) or family boundary ambiguity.(51) Several studies were aimed at testing

the impact of only one particular symptom/symptom cluster on caregiver mental health (e.g., wandering,(70) delusions,(49) depression,(57;66) and sundowning(68)), and therefore could not make hypotheses about the relative effect of multiple symptoms. Investigators who tested the impact of more than one symptom (e.g., aggression *and* agitation(75)) on caregiver outcomes did not hypothesize as to whether one symptom would have a greater impact on caregivers than another.

Dynamic relationships over time

Although the majority of studies were cross-sectional in nature, seven papers (20%) examined the relationship between individual symptoms and outcomes over multiple time points; three(51;66;75) examined caregiver depression as an outcome, three(67-69) examined caregiver burden as an outcome, and one(44) examined both outcomes over time. No consistent patterns could be discerned from these studies due to the overall small number of longitudinal studies conducted, and given the studies' disparate aims relative to the role of behavior timing and wide variation in the number of time points assessed, period of time studied, and stage of disease/caregiving relationship. Yet these study findings suggest that the timing of behaviors may impact the relationship between BPSD and caregiver outcomes. First, specific behaviors may have more negative effects for caregivers at certain points in the caregiver-patient relationship. For example, Berger et al,(44) found that across five time points, specific BPSD had varying associations with caregiver burden and depression (e.g., patient sleep disturbances were only correlated with caregiver depression at 24 months). Second, there is some evidence to suggest that there may be sensitive time periods in which patients' symptoms may have lasting impact on caregiver outcomes. Elmstahl et al,(67) examined individual BPSD features at varying time points and found that lack of vitality (i.e., tiredness) during transition to group

living facility affected caregiver outcomes 12 months later. Additionally, authors found that initial sundowning behaviors affected increase in stress over time.(68) Danhauer et al., (75), however, did not find baseline behaviors to impact subsequent caregiver behaviors. Finally, findings from two studies suggest that change in patient behaviors may impact change in caregiver outcomes.(51;66)

Source of heterogeneity of findings

Because we were unable to identify any individual patient symptom(s) that consistently negatively impacted caregivers, we examined a variety of study characteristics and the overall quality of the studies reviewed as potential explanations for the heterogeneity of findings. First, we examined study setting variation given the wide range of international settings in which study samples were drawn. Only one-third of studies examined were U.S.-based; the remainder were from Europe (n=8, 23%), Asia (n=6, 17%); Canada (n=6, 17%), Australia (n=2, 6%), and South America (n=1, 3%). When limiting the sample to those studies with large, U.S.-based samples (n>100) with caregiver depression as an outcome (n=4), we still find the following range of symptoms associated with caregiver outcomes: anger/aggressiveness,(25) emotional lability,(14) psychosis,(61) and depression.(61;66) Although we reviewed studies published over a 20 year time period, we did not find any variations in findings due to when the study was published. Furthermore, like most caregiving studies, the studies examined were almost entirely clinic-based samples, recruited from memory clinics or hospitals, assisted living facilities, or via caregivers' support groups. When we restricted our review to studies with population samples,(25;46;69) we continued to find inconsistent patterns of impactful symptoms. The majority of studies included patients with a mix of dementia diagnoses or unspecified dementia or cognitive impairment (see Tables 1.1-1.2). Among those studies that focused examination on

patients with AD (n=12)(12;14;47;49;53;56;57;61;73-75;94) we did not find symptoms that consistently impacted caregiver burden or depression. Finally, the vast majority of studies did not consider effect modifiers such as race/ethnicity which may have impact on the experience of specific symptoms. Harwood et al,(61) for example, concluded that patient psychosis had a greater impact on depression in white non-Hispanic spouses compared to Hispanic spouses.

Next, we examined overall study quality to determine whether factors such as small sample size and lack of control for potential confounding limited our ability to find consistently impactful BPSD symptoms. Half of the studies included sample sizes of 100 dyads or less, which impacts ability to detect smaller effect sizes. The median sample size across the 35 studies was 107, and only four studies included more than 300 dyads.(25;46;61;66) Furthermore, among studies included in this review, most did not control for important confounders such as functional status, in part due to small sample size. Overall, there was a lack of utilization of statistical analyses to control for additional covariates: twenty-six percent used unadjusted correlation analyses (n=6),(12;44;45;51;68;72) chi-square tests (n=2),(49;50) or paired t-tests (n=1)(69) to examine patient-caregiver associations. Control for such factors would have weakened observed associations and may account for why so many individual symptoms were found to negatively impact caregivers. Furthermore, studies did not simultaneously control for the full range of BPSD symptoms, even if they successfully adjusted for the effects of multiple covariates. For example, Covinsky et al,(25) controlled for important patient and caregiver characteristics including patient functional status using data from a large population-based study. While this study found that anger/aggression and danger to self or others were important predictors of caregiver depression, it unfortunately only tested three individual patient behaviors in total, failing to simultaneously consider the range of behaviors that are important stressors for

caregivers. Similarly, while Neundorfer et al(66) used multilevel analysis with a sample of 353 dyads to show that over five years increase in patient depressive symptoms predicted increase in caregiver depressive symptoms, the study did not control for the effect of patient BPSD symptoms other than depression that may have changed over time and influenced caregiver outcomes.

Discussion

The literature has successfully revealed that BPSD negatively impacts caregiver outcomes. We undertook this review in order to determine if there is evidence to suggest that individual BPSD symptoms differentially impact caregiver outcomes. This review identified more than 600 articles that addressed the issue of patient behavior problems and caregiver outcomes; most did not examine individual symptoms, and instead aggregated behaviors into one measure of BPSD such that each symptom is equally contributing to what is considered an objective burden for the caregiver. While it is clear that BPSD, in general, and many individual symptoms are associated with negative caregiver outcomes, the evidence remains inconclusive as to whether some symptoms are more important than others. While we did find specific symptoms, namely, (1) depression, (2) aggression, and (3) sleep disturbances, to be commonly cited as impactful there were no individual symptom/symptom cluster(s) that were consistently tested and found to result in negative outcomes for caregivers. In fact, most symptom types were reported as having a negative impact on caregivers in at least one study.

Furthermore, the most commonly cited impactful symptoms were also those most frequently tested. While most studies tested a range of symptoms patients with dementia are known to exhibit, several studies were specifically designed to test the impact of one specific

symptom/symptom cluster (e.g. wandering,(70) delusions,(49) depression,(57;66) and sundowning(68)) on caregiver outcomes). While we included these studies in our review, they do not examine the impact of one symptom relative to others, and their inclusion makes the pool of symptoms examined less representative of all possible dementia behaviors. When we examined which symptoms were most often found to be impactful relative to how often they were tested, we found that anxiety, activity disturbances, and disruptive behaviors were always found to be impactful and paranoia, repetitive behavior, and agitation had significant impact 75% of the time. However, because none of these symptoms were examined by more than four studies, they were not commonly cited as impactful to caregivers among all papers reviewed. This discrepancy further substantiates our conclusion that research has yet to elucidate whether there are individual symptoms/symptom cluster(s) which result in the most negative outcomes for caregivers.

Limitations

We did not re-categorize symptoms across studies when assessing frequency of symptoms cited as impactful. Thus, the categorization scheme used within each study (i.e., how symptoms are categorized within a study) impacts these findings. Even within individual studies, researchers reported different findings from models that incorporated broader subscales than models that included individual items. For example, when examining predictors of caregiver depression, Victoroff et al.(43) found that non-aggressive agitation as a subscale was predictive of caregiver depression, but when examining 29 individual agitation items, specific aggressive behaviors, namely making sexual advances and destroying property, were most predictive. Depression and aggression are broader symptom categories than specific behaviors such as hiding things and hitting. While the latter symptoms were analyzed in this review as separate items, they may in

fact be referring to similar constructs. Re-categorizing more specific behaviors/symptoms into broader categories could have impacted these findings.

While we initially planned to limit this review to studies that focused on caregiver depression as an outcome as depression is a well-studied construct with clear impact on an individual's health, because of the limited number of published studies examining individual symptoms, we included caregiver burden studies as well. While we first reviewed these outcomes separately, we ultimately grouped them together after finding no differences between them. A wide range of assessments were used to measure depression and burden. Within our review, researchers used nine different measures of caregiver depression and at least 13 different measures of caregiver burden (including one clinical assessment of burden (63)). The use of a wide range of outcome measures may also contribute to inconsistent findings. Again, because of a lack of studies published, we were unable to limit this review to studies that measured depressive symptoms using similar assessments. Finally, we relied on a synthesis approach for this study which effectively relies on a count of significant and non-significant effects. Because of the limited number of studies meeting inclusion criteria, heterogeneity in study design and study measurements, meta-analyses techniques could not be employed to examine pooled estimates of effect.

Implications and recommendations

An extensive body of research provides robust evidence suggesting that overall BPSD exert negative impact on caregiver outcomes. The next step, not yet addressed in the literature, is to determine whether and how individual symptom clusters differentially impact the caregiver. Based on this review, we recommend that future research build upon existing knowledge of the

relationship between BPSD and caregiving and consider the following issues to identify whether there are individual symptoms of BPSD that are most challenging to caregivers:

1. Categorizing BPSD based on the caregiver's perspective

Existing studies categorized BPSD based on how they manifest within the patient and not based on how they impact the caregivers, despite the fact that caregiver depression or burden were the outcomes of interest in the studies reviewed. Behaviors tend to be grouped together in order to describe clinical symptoms using similar domains used for non-dementia patients (e.g., psychotic vs. mood symptoms) or based on how they empirically cluster within the dementia patient.

While these classifications may be useful for understanding potential varying etiologies of BPSD syndromes (e.g., Aalten et al.(95)) and for assessing patient treatment options, they may not be fully capturing the impact of the behaviors on the caregiver. Each member of the patient-caregiver dyad is impacted by BPSD, but not necessarily in the same way. Major events can differentially impact patients and caregivers; nursing home placement, for example, has positive effects for caregivers such as decreased stress but negative repercussions for patients including increased mortality. Therefore, researchers should begin to conceptualize BPSD components from the perspective of how they might impact the caregiver and consider how a behavior or symptom may differentially impact the caregiver and patient. For example, given the fact that psychotic behaviors are often unexpected and may be frightening to the caregivers who perceive them as non-normative, psychosis may have relatively little impact on quality of life for the patient, but may have huge implications for the well-being of the overwhelmed caregiver.

2. Delineating causal mechanisms

Studies have not identified pathways for the association between an individual symptom and caregiver outcomes. Further research is necessary to understand if and why individual behaviors or symptoms may have greater negative mental health consequences by operating through different pathways. While research suggests that the association between BPSD in general and mental and physical health outcomes of caregivers are mediated by subjective stress appraisal,(15;96;97) it is not yet clear by which pathway individual symptoms ultimately result in negative caregiver outcomes. In addition to subjective stress, other pathways may be part of this process and should be further studied using mediation analysis.

3. The role of time and timing

While the majority of studies were cross-sectional, and the longitudinal studies reviewed were highly heterogeneous in aims and methodology, some evidence suggests that timing of BPSD over the course of the patient-caregiver relationship may impact caregiver outcomes. While this review suggests that certain symptoms may be of particular importance over time, and that specific time periods may be important to focus on, the paucity of studies evaluating the issue highlights a clear need for further study.

4. Emphasis on stage of illness

The vast majority of studies reviewed do not specify and control for stage of disease in assessing the relationship between symptoms and caregiver outcomes. Authors rarely examined stage of dementia illness except to systematically exclude institutionalized patients, who typically have the most advanced diseases. We found that only five studies (14;43;48;49;51) indicated that they restricted the sample to patients at a specific stage/stages of illness (e.g., mild to moderate or moderate to severe). Although controlling for cognitive status (one marker of disease

progression), was a common technique used to address this issue, such an approach unfortunately may not succeed in capturing how long the patient has been suffering with illness or impairment, a construct critical to caregiver outcomes. Grouping together dementia patients at all stages of disease progression may be problematic as disease stage impacts caregiver outcomes.(10) Gonzalez-Salvador et al, for example, finds that the associations between caregiver stress and individual behaviors in mild, moderate and severe AD subgroups differ substantially.(47) While the authors concluded that aggression was most important for all stages of AD, delusional ideation was independently associated with stress for those with mild and moderate AD, but not for those with severe AD. Future research in this area should consider the impact of disease stage in analyses.

5. Diagnostic context

Additionally, studies have not differentiated between dementia subtypes. While our study excluded samples that focused exclusively on less common subtypes of dementia (e.g., Dementia with Lewy Bodies and Frontotemporal Dementia), only one third of studies were restricted to patient samples who exclusively had diagnoses of AD (e.g., Donaldson et al.(13)). BPSD symptoms emerge in the context of different subtypes of dementia, which have widely varied prevalence and trajectory of behavior symptoms.(98) Etiology of dementia, or diagnostic context, may influence the way that caregivers experience psychiatric features of dementia. According to attribution theory, perceptions of controllability of behaviors influence the emotional reaction of caregivers.(99) In other words, caregivers who perceive patients as having less control over their behaviors have a less emotional response and less negative affect. This relationship has been tested within the context of aging. Using vignette experiments, researchers found that disruptive behavior attributed to AD compared to aging alone or even depression was

perceived as (1) more biological in nature, (2) less controllable by the patient, and (3) more likely to garner sympathy from the caregiver.(100) Diagnostic context may therefore play a role in explaining the relationship between BPSD and caregiver depression such that those caregivers who attribute more behaviors to disease are less likely to experience negative outcomes. Testing these relationships across varied disease contexts can add to our understanding of how BPSD affect caregivers and ultimately impact disease-specific intervention design.

Conclusion

Our review finds that despite the consistency of the association between BPSD and caregiver depression and burden within the existing literature, research has not focused on examining whether and how specific symptoms or groups of symptoms differentially impact caregiver outcomes. Moreover, very few studies have examined how these relationships change over time. In order to determine the key ingredients in BPSD that result in negative mental health for caregivers, we need studies that not only are designed to examine differences among BPSD symptom clusters, but specifically categorize BPSD based on how they negatively affect caregivers. Additionally, we recommend that studies examine casual mechanisms by which individual BPSD impact caregivers and consider stage of disease, and the role of different subtypes of dementia in future research. Such an approach will help to elucidate whether individual BPSD differentially impact caregivers and allow for focused intervention and treatments efforts that benefit the patient-caregiver dyad.

Table 1.1: Publications that examine association between individual BPSD symptom clusters and caregiver depression/ depressive symptoms published 1990-2010 (n=17)

Study (Authors, date, reference number)	Study design	Setting	Population	Diagnosis	Sample size	Symptom scale used	CG depression scale used	Symptoms examined
Asada et al 2000(73)	CS	Asia	mixed	AD	107	Troublesome Behavior Scale (TBS)	General Health Questionnaire (GHQ)	Agitation* Hyperactivity Miscellaneous
Ballard et al 1995(64)	Case-control	Europe	clinic sample	dementia	109	Carers Stress Scale	Cornell Depression Scale	Aggression Depression Restlessness Sleep problems Suspiciousness
Berger et al 2005(44)	Longitudinal	Europe	clinic sample	dementia	45	BEHAVE-AD	Beck Depression Inventory (BDI) Geriatric Depression Scale (GDS)	Activity disturbances Aggression Affective disturbances Anxiety Psychotic symptoms Sleep disturbances*
Brodsky & Luscombe 1998(65)	CS	Australia	clinic sample	dementia	193	Problem Behavior Checklist (demanding behavior subscale), Hamilton Rating Scale for Depression (Ham-D)	GHQ	Demanding/difficult behaviors* Depression*
Caron et al 1999(51)	Longitudinal	U.S.	mixed	dementia (mild to moderate)	72	BEHAVE -AD	Zung Caregiver Depression (Zung)	Activity disturbances* Anxiety* Depression Paranoia*

Chappell & Penning, 1996(46)	CS	Canada	population sample	dementia	327	Dementia Behavior Disturbance Scale (DBD)	CES-D	Aggression Aimlessness Apathy* Inappropriate sexual behavior Lack of cooperation Restlessness
Covinsky et al 2003(25)	CS	U.S.	population sample	dementia	5627	Not stated	GDS	Anger/aggression * Danger to self or others * Wakes caregiver at night
Croog et al 2006 (14)	CS	U.S.	clinical trial	AD (mild to moderate)	199	Memory and Behavior Problem Checklist (MBPC) Sandoz Clinical Assessment-Geriatric (SCAG)	General well being adjustment scale (depression subscale)	Destructive behaviors Emotional lability* Personal care problems
Danhauer et al 2004 (75)	Longitudinal	U.S.	clinic sample	AD	90	Patient Behavior Checklist (select items)	CES-D	Agitation Aggression*
Donaldson et al 1998(13)	CS	Europe	clinic sample	AD	100	Cornell Scale for Depression in Dementia (CSDD) Manchester and Oxford Scale For Psychopathology Assessment In Dementia	GHQ	Aggression Depression* Emotional lability Psychotic symptoms* Sleep disturbances* Various individual psychotic behaviors
Harwood et al 1998(61)	CS	U.S.	clinic sample	AD	653	clinical diagnosis of depression and psychosis	CES-D	Depression* Psychosis*
Heok et al 1997(52)	CS	Asia	clinic sample	dementia	50	BEHAVE -AD	GHQ	Depression*
Levesque et al 1995 (76)	CS	Canada	mixed	dementia	265	Revised Memory and Behavior Problem Checklist (RMBPC)	Brief Symptom Inventory (BSI)	Depression Disruptive behaviors*

LoGiudice et al 1995(45)	CS		Australia	clinic sample	dementia	24	CAMDEX	GHQ	Depression* Paranoia Personality changes* Sleep disturbances*
Mahoney et al 2005(53)	CS		Europe	population	AD	153	NPI, GDS	Hospital Anxiety and Depression Scale (HADS)	Aberrant motor behaviors Agitation/aggression Anxiety Apathy Delusions Depression Disinhibition/Acting out Euphoria Hallucinations Irritability*
Neundorfer et al 2001(66)	Longitudinal		U.S.	clinic sample	dementia	353	Behavior Rating Scale for Depression (BRSD-DEP)	CES-D	Depression*
Victoroff et al 1998(43)	CS		U.S.	clinic sample	Dementia (early to middle stages)	35	CMAI, CSDD, BEHAVE-AD (select items)	Zung	Agitation (various individual items)* Delusions Depression Hallucinations

* Symptom determined to be impactful in study
CS= Cross-sectional

Table 1.2: Publications that examine association between individual BPSD symptom clusters and caregiver burden published 1990-2010 (n=23)

Study/studies (Authors, date, reference number)	Study design	Setting	Population	Diagnosis	Sample size	Symptom instrument used	CG burden scale used	Symptoms examined
Allegri et al 2006(12)	CS	South America	clinic sample	AD	82	NPI	Zarit Burden Interview (ZBI)	Agitation/ aggression Anxiety* Apathy Delusions Disinhibition/Acting out Depression Euphoria Hallucinations* Irritability Sleep disturbances* Unusual motor behaviors*
Bedard et al 2005(56)	CS	Canada	clinic sample	AD	557	GDS Dysfunctional Behavior Rating Instrument (DBRI)	ZBI	Depression Emotional behaviors* Demanding/difficult behaviors* Psychotic behaviors Repetitive behavior*
** Berger et al 2005 (44)	Longitudinal	Europe	clinic sample	dementia	45	BEHAVE-AD	Caregiver Burden Interview (CBI)	Activity disturbances* Affective disturbances Aggression* Anxiety* Psychotic symptoms Sleep disturbances
** Chappell & Penning, 1996(46)	CS	Canada	population	dementia	327	DBD	ZBI	Apathy* Aimlessness* Aggression* Restlessness*

** Donaldson et al 1998(13)	CS	Europe	clinic sample	dementia	100	CSDD, Manchester and oxford scale for psychopath assessment in dementia	Gilleard's strain scale	Aggression Depression* Emotional lability Psychotic symptoms Sleep disturbances Various individual psychotic behaviors
Elmstahl et al 1998(67)	Longitudinal	Europe	clinic sample	dementia	64	Confusion Scale Hallucinations- Syncope Index Lack of Vitality Index Clinical Variations Index	Not stated	Clinical variations (mood etc) Confusion Hallucinations Lack of vitality* Syncope
Gallagher-Thompson et al 1992(68)	Longitudinal	U.S.	clinic sample	dementia	35	Behavioral Disturbance Questionnaire (BDQ) (sundowning only)	Perceived Stress Scale (PSS)	Sundowning*
Gonzalez-Salvador et al 1999(47)	Case-control	Europe	clinic sample	AD	67	BEHAVE-AD	Relative's Stress Scale (RSS)	Aggression* Activity disturbance Affective symptoms Anxiety Delusions Hallucinations Sleep disturbances

Grafstrom & Winblad 1998(69)	Longitudinal	Europe	population	dementia	219	CAMDEX	Not stated	Hiding things* Paranoia* Sleep disturbances* Depression*
Hadjstavropoulis et al 1994 (57)	CS	Canada	clinic sample	AD	136	GDS Present Functioning Questionnaire (PFO) (dysphoria only)	ZBI	
Lim et al 1999 (63)	CS	Asia	clinic sample	dementia	93	various individual behaviors	clinician assessment	Aggression Agitation Apathy Repetitive behavior* Stripping Wandering*
Lim et al 2008(70)	CS	Asia	clinic sample	dementia	83	Korean Wandering Scale	Caregiver Worry Overload Role Captivity Scale	Wandering*
**LoGiudice et al 1995(45)	CS	Australia	clinic sample	dementia	24	CAMDEX	Family Burden Interview	Depression* Paranoia* Personality changes* Sleep disturbances*
Magai & Cohen 1998(48)	CS	U.S.	clinic sample	dementia (middle to late stage)	168	BEHAVE -AD	ZBI	Activity disturbances Affective symptoms Anxiety Delusions Depression* Hallucinations Sleep disturbances

Molloy et al 1996(58)	CS	Canada	clinic sample	Cognitive impairment	108	GDS Dysfunctional Behavior Rating Instrument (DBRI)	ZBI	Disinhibition/Acting out* Delusions Depression Disruptive behavior* Frustration/crying* Hallucinations Repetitive behaviors
Onishi et al 2005(62)	CS	Asia	clinic sample	None (elderly patients)	116	various individual behaviors	ZBI	Depression* Disturbing conversation* (33 additional individual symptoms examined)
Reis et al 1994(71)	CS	Canada	mixed	dementia	213	MBPC Ryden Aggression Scale	ZBI	Aggression*
Riello et al 2002(49)	CS	Europe	clinic sample	AD (mild)	43	NPI	NPI -distress	Delusions*
Robinson et al 2001(72)	CS	U.S.	mixed	dementia	30	RMBPC	Cost of Care Index	Depression Disruptive behaviors*
Rymer et al 2002(94)	CS	U.S.	clinic sample	AD	41	Frontal Systems Behavior Scale	ZBI	Apathy Disinhibition/Acting out* Executive dysfunction
Shaji et al 2009(50)	CS	Asia	population	dementia	29	BEHAVE -AD	BEHAVE -AD (caregiver distress rating)	Activity disturbances* Affective symptoms Aggression* Anxiety Delusions* Hallucinations Sleep disturbances
Tun et al 2008(74)	CS	U.S.	clinic sample	AD	122	NPI	Screen for Caregiver Burden Scale	Affective symptoms* Apathy Highly symptomatic symptoms*

**Victoroff et al 1998(43)	CS	U.S.	clinic sample	dementia (early to middle stage)	35	CMAI CSDD BEHAVE-AD (select items)	ZBI	Aggression* Agitation (various individual items) Delusions Depression Hallucinations
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* Symptom determined to be impactful in study

**Study also listed in Table 1.1

CS= Cross-sectional

Table 1.3: Individual patient symptoms that negatively impact caregiver burden and depression*

Symptom/ symptom cluster	No. studies examined by n	No. studies in which behavior negatively impacts caregivers		
		Total n (study #)	Depression studies n (study #)	Burden studies n (study #)
Depression	25	10(13;45;45;48;52;57;62;65;66;73)	6(13;45;52;65;66;73)	4(45;48;57;62)
Anger/aggression	16	8(25;43;44;46;47;50;63;71;75)	2(25;75)	6(43;44;46;47;50;63;71)
Sleep disturbances	14	6(12;13;44;45;45;69)	3(13;44;45)	3(12;45;69)
Activity disturbances	3	3(44;50;51)	1 (51)	2(44;50)
Anxiety	3	3(12;44;51)	1 (51)	2 (12;44)
Disruptive behavior	3	3(58;72;76)	1 (76)	2(58;72)
Paranoia	4	3(45;51;69)	1 (51)	2(45;69)
Repetitive behavior	4	3(43;56;63)		3(43;56;63)
Agitation	4	3(43;73)	2(43;73)	1(73)
Apathy	3	2(46)	1(46)	1(46)
Delusions	7	2(49;50)		2(49;50)
Demanding/difficult behavior	2	2(56;65)	1(56)	1(65)
Disinhibition/ acting out	4	2(58;94)		2(58;94)
Personality changes	2	2(45)	1(45)	1(45)
Psychosis	3	2(13;61)	2(13;61)	
Affective symptoms	3	1(74)		1(74)
Aimlessness	1	1(46)		1(46)
Danger to self	1	1(25)	1(25)	
Destroying property	1	1(43)	1(43)	
Disturbing conversation	1	1(62)		1(62)
Emotional behavior	1	1(56)		1(56)
Emotional lability	1	1(14)	1(14)	
Frustration/ crying	1	1 (58)		1 (58)
Hallucinations	6	1(12)		1(12)
Hiding things	1	1(69)		1(69)
Highly symptomatic symptoms	1	1(74)		1(74)
Hitting	1	1(43)		1(43)
Inappropriate dressing	1	1(43)	1(43)	
Irritability	1	1(53)	1(53)	
Lack of vitality	1	1(67)		1(67)
Restlessness	1	1(46)		1(46)
Sexual advances	1	1(43)	1(43)	
Sundowning	1	1(68)		1(68)
Unusual motor behavior	1	1(12)		1(12)
Wandering	2	1(70)		1(70)

* Symptoms associated with multiple outcomes (caregiver depression and burden) within individual studies are counted more than once when applicable.

References

- (1) Gaugler JE, Kane RA, Langlois J. Assessment of family caregivers of older adults. In: Kane RL, Kane RA, eds. *Assessing Older Persons: Measures, Meaning and Practical Applications*. New York: Oxford University Press, 2003:320-359.
- (2) National Alliance for Caregiving, AARP. *Caregiving in the U.S.* Washington, DC: AARP; 2004.
- (3) Schulz R, O'Brien AT, Bookwala J, Fleissner K. Psychiatric and physical morbidity effects of dementia caregiving: prevalence, correlates, and causes. *Gerontologist* 1995 Dec;35(6):771-791.
- (4) 2009 Alzheimer's disease facts and figures. *Alzheimers Dement* 2009 May;5(3):234-270.
- (5) Black W, Almeida OP. A systematic review of the association between the Behavioral and Psychological Symptoms of Dementia and burden of care. *Int Psychogeriatr* 2004 Sep;16(3):295-315.
- (6) Pinquart M, Sorensen S. Associations of stressors and uplifts of caregiving with caregiver burden and depressive mood: a meta-analysis. *J Gerontol B Psychol Sci Soc Sci* 2003 Mar;58(2):112-128.
- (7) Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. *Gerontologist* 1980 Dec;20(6):649-655.
- (8) Clyburn LD, Stones MJ, Hadjistavropoulos T, Tuokko H. Predicting caregiver burden and depression in Alzheimer's disease. *J Gerontol B Psychol Sci Soc Sci* 2000 Jan;55(1):S2-13.
- (9) Meshefedjian G, McCusker J, Bellavance F, Baumgarten M. Factors associated with symptoms of depression among informal caregivers of demented elders in the community. *The Gerontologist* 1998 Apr;Vol.38(2):247-253.
- (10) Ballard C, Lowery K, Powell I, O'Brien J, James I. Impact of behavioral and psychological symptoms of dementia on caregivers. *International Psychogeriatrics* 2000;Vol.12(Suppl1):93-105.
- (11) Donaldson C, Tarrier N, Burns A. The impact of the symptoms of dementia on caregivers. *Br J Psychiatry* 1997 Jan;170:62-68.
- (12) Allegri RF, Sarasola D, Serrano CM, et al. Neuropsychiatric symptoms as a predictor of caregiver burden in Alzheimer's disease. *Neuropsychiatr Dis Treat* 2006 Mar;2(1):105-110.
- (13) Donaldson C, Tarrier N, Burns A. Determinants of carer stress in Alzheimer's disease. *International Journal of Geriatric Psychiatry* 1998 Apr;Vol.13(4):248-256.

- (14) Croog SH, Burleson JA, Sudilovsky A, Baume RM. Spouse caregivers of Alzheimer patients: problem responses to caregiver burden. *Aging Ment Health* 2006 Mar;10(2):87-100.
- (15) Hooker K, Bowman SR, Coehlo DP, et al. Behavioral change in persons with dementia: relationships with mental and physical health of caregivers. *J Gerontol B Psychol Sci Soc Sci* 2002 Sep;57(5):453-460.
- (16) de Vugt ME, Stevens F, Aalten P, et al. Behavioural disturbances in dementia patients and quality of the marital relationship. *Int J Geriatr Psychiatry* 2003 Feb;18(2):149-154.
- (17) Haley WE, Brown SL, Levine EG. Family Caregivers Appraisals of Patient Behavioral Disturbance in Senile Dementia. *Clinical Gerontologist* 1987;6(4):25-34.
- (18) Schulz R, Williamson GM. A 2-year longitudinal study of depression among Alzheimer's caregivers. *Psychol Aging* 1991 Dec;6(4):569-578.
- (19) Aneshensel CS, Pearlin LI, Mullan J.T., Zarit SH, Whitlach C.J. Profiles in caregiving: The unexpected career. San Diego: Academic Press, 1995.
- (20) Cullen JS, Grayson DA, Jorm AF. Clinical diagnoses and disability of cognitively impaired older persons as predictors of stress in their carers. *Int J Geriatr Psychiatry* 1997 Oct;12(10):1019-1028.
- (21) Teri L. Behavior and caregiver burden: behavioral problems in patients with Alzheimer disease and its association with caregiver distress. *Alzheimer Dis Assoc Disord* 1997;11 Suppl 4:S35-S38.
- (22) Dunkin JJ, Anderson-Hanley C. Dementia caregiver burden: a review of the literature and guidelines for assessment and intervention. *Neurology* 1998 Jul;51(1 Suppl 1):S53-S60.
- (23) Gaugler JE, Davey A, Pearlin LI, Zarit SH. Modeling caregiver adaptation over time: the longitudinal impact of behavior problems. *Psychol Aging* 2000 Sep;15(3):437-450.
- (24) Yaffe K, Fox P, Newcomer R, et al. Patient and caregiver characteristics and nursing home placement in patients with dementia. *JAMA* 2002 Apr 24;287(16):2090-2097.
- (25) Covinsky KE, Newcomer R, Fox P, et al. Patient and caregiver characteristics associated with depression in caregivers of patients with dementia. *J Gen Intern Med* 2003 Dec;18(12):1006-1014.
- (26) Baumgarten M, Hanley JA, Infante-Rivard C, Battista RN, Becker R, Gauthier S. Health of family members caring for elderly persons with dementia. A longitudinal study. *Ann Intern Med* 1994 Jan 15;120(2):126-132.
- (27) Brodaty H. Caregivers and behavioral disturbances: effects and interventions. *Int Psychogeriatr* 1996;8 Suppl 3:455-458.

- (28) Zarit SH. Behavioral disturbances of dementia and caregiver issues. *Int Psychogeriatr* 1996;8 Suppl 3:263-268.
- (29) Coen RF, Swanwick GR, O'Boyle CA, Coakley D. Behaviour disturbance and other predictors of carer burden in Alzheimer's disease. *Int J Geriatr Psychiatry* 1997 Mar;12(3):331-336.
- (30) Haley WE. The family caregiver's role in Alzheimer's disease. *Neurology* 1997 May;48 (5 Suppl 6):S25-S29.
- (31) Bedard M, Pedlar D, Martin NJ, Malott O, Stones MJ. Burden in caregivers of cognitively impaired older adults living in the community: methodological issues and determinants. *Int Psychogeriatr* 2000 Sep;12(3):307-332.
- (32) Bookwala J, Schulz R. A comparison of primary stressors, secondary stressors, and depressive symptoms between elderly caregiving husbands and wives: the Caregiver Health Effects Study. *Psychol Aging* 2000 Dec;15(4):607-616.
- (33) Li LW, Seltzer MM, Greenberg JS. Social support and depressive symptoms: differential patterns in wife and daughter caregivers. *J Gerontol B Psychol Sci Soc Sci* 1997 Jul;52(4):S200-S211.
- (34) Burns A. The burden of Alzheimer's Disease. *Int J Neuropsychopharm* 2000;3:31-38.
- (35) Burns A. Behavioral and psychological symptoms of dementia and caregiver burden. *Int Psychogeriatr* 2000;12(Suppl 1):347-350.
- (36) Chui HC, Lyness SA, Sobel E, Schneider LS. Extrapyrarnidal signs and psychiatric symptoms predict faster cognitive decline in Alzheimer's disease. *Arch Neurol* 1994; 51:676-681. *Arch Neurol* 1994;51:676-681.
- (37) Scarmeas N, Brandt J, Albert M, et al. Delusions and hallucinations are associated with worse outcome in Alzheimer disease. *Arch Neurol* 2005 Oct;62(10):1601-1608.
- (38) Scarmeas N, Brandt J, Blacker D, et al. Disruptive behavior as a predictor in Alzheimer disease. *Arch Neurol* 2007 Dec;64(12):1755-1761.
- (39) Davis LL, Buckwalter K, Burgio LD. Measuring problem behaviors in dementia: developing a methodological agenda. *ANS Adv Nurs Sci* 1997 Sep;20(1):40-55.
- (40) Aalten P, de Vugt ME, Jaspers N, Jolles J, Verhey FR. The course of neuropsychiatric symptoms in dementia. Part II: relationships among behavioural sub-syndromes and the influence of clinical variables. *Int J Geriatr Psychiatry* 2005 Jun;20(6):531-536.
- (41) Aalten P, de Vugt ME, Jaspers N, Jolles J, Verhey FR. The course of neuropsychiatric symptoms in dementia. Part I: findings from the two-year longitudinal Maasbed study. *Int J Geriatr Psychiatry* 2005 Jun;20(6):523-530.

- (42) Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994 Dec;44(12):2308-2314.
- (43) Victoroff J, Mack WJ, Nielson KA. Psychiatric complications of dementia: impact on caregivers. *Dement Geriatr Cogn Disord* 1998 Jan;9(1):50-55.
- (44) Berger G, Bernhardt T, Weimer E, Peters J, Kratzsch T, Frolich L. Longitudinal study on the relationship between symptomatology of dementia and levels of subjective burden and depression among family caregivers in memory clinic patients. *Journal of Geriatric Psychiatry & Neurology* 2005 Sep;18(3):119-128.
- (45) LoGiudice D, Waltrowicz W, McKenzie S, Ames D, Flicker L. Prevalence of dementia among patients referred to an aged care assessment team and associated stress in their carers. *Aust J Public Health* 1995 Jun;19(3):275-279.
- (46) Chappel NL, Penning M. Behavioural problems and distress among caregivers of people with dementia. *Ageing and Society* 1996;16:57-73.
- (47) Gonzalez-Salvador MT, Arango C, Lyketsos CG, Barba AC. The stress and psychological morbidity of the Alzheimer patient caregiver. *International Journal of Geriatric Psychiatry* 1999 Sep;Vol.14(9):701-710.
- (48) Magai C, Cohen CI. Attachment style and emotion regulation in dementia patients and their relation to caregiver burden. *J Gerontol B Psychol Sci Soc Sci* 1998 May;53(3):147-154.
- (49) Riello R, Geroldi C, Zanetti O, Frisoni GB. Caregiver's distress is associated with delusions in Alzheimer's patients. *Behav Med* 2002;28(3):92-98.
- (50) Shaji KS, George RK, Prince MJ, Jacob KS. Behavioral symptoms and caregiver burden in dementia. *Indian J Psychiatry* 2009 Jan;51(1):45-49.
- (51) Caron W, Boss P, Mortimer J. Family boundary ambiguity predicts Alzheimer's outcomes. *Psychiatry* 1999;62(4):347-356.
- (52) Heok KE, Li TS. Stress of caregivers of dementia patients in the Singapore Chinese family. *International Journal of Geriatric Psychiatry* 1997 Apr;Vol.12(4):466-469.
- (53) Mahoney R, Regan C, Katona C, Livingston G. Anxiety and depression in family caregivers of people with Alzheimer disease: the LASER-AD study. *Am J Geriatr Psychiatry* 2005 Sep;13(9):795-801.
- (54) Reisberg B, Auer SR, Monteiro IM. Behavioral pathology in Alzheimer's disease (BEHAVE-AD) rating scale. *Int Psychogeriatr* 1996;8 Suppl 3:301-308.

- (55) Teri L, Truax P, Logsdon R, Uomoto J, Zarit S, Vitaliano PP. Assessment of behavioral problems in dementia: the revised memory and behavior problems checklist. *Psychol Aging* 1992 Dec;7(4):622-631.
- (56) Bedard M, Kuzik R, Chambers L, Molloy DW, Dubois S, Lever JA. Understanding burden differences between men and women caregivers: the contribution of care-recipient problem behaviors. *Int Psychogeriatr* 2005 Mar;17(1):99-118.
- (57) Hadjistavropoulos T, Taylor S, Tuokko H, Beattie BL. Neuropsychological deficits, caregivers' perception of deficits and caregiver burden. *J Am Geriatr Soc* 1994 Mar;42(3):308-314.
- (58) Molloy DW, Lever R, Bedard M, Guyatt G, Butt G. Burden in care-givers of older adults with impaired cognition: The relationship with dysfunctional behaviors, daily living and mood. *Annals RCPSC* 1996 Nov 11.
- (59) Brink TL, Yesavage JA, Lum O, Heersema P, Adey MB, Rose TL. *Clinical Gerontologist* 1982;1:37-44.
- (60) Cohen-Mansfield J. Measurement of inappropriate behavior associated with dementia. [Review] [51 refs]. *Journal of Gerontological Nursing* 25(2):42-51, 1999 Feb.
- (61) Harwood DG, Barker WW, Cantillon M, Loewenstein DA, Ownby R, Duara R. Depressive symptomatology in first-degree family caregivers of Alzheimer disease patients: a cross-ethnic comparison. *Alzheimer Dis Assoc Disord* 1998 Dec;12(4):340-346.
- (62) Onishi J, Suzuki Y, Umegaki H, Nakamura A, Endo H, Iguchi A. Influence of behavioral and psychological symptoms of dementia (BPSD) and environment of care on caregivers' burden. *Arch Gerontol Geriatr* 2005 Sep;41(2):159-168.
- (63) Lim PPJ, Sahadevan S, Choo GK, Anthony P. Burden of caregiving in mild to moderate dementia: An Asian experience. *International Psychogeriatrics* 1999 Dec;Vol.11(4):411-420.
- (64) Ballard CG, Saad K, Coope B, et al. The aetiology of depression in the carers of dementia sufferers. *Journal of Affective Disorders* 1995 Oct 9;35(1-2):59-63.
- (65) Brodaty H, Luscombe G. Psychological morbidity in caregivers is associated with depression in patients with dementia. *Alzheimer Dis Assoc Disord* 1998 Jun;12(2):62-70.
- (66) Neundorfer MM, McClendon MJ, Smyth KA, Stuckey JC, Strauss ME, Patterson MB. A longitudinal study of the relationship between levels of depression among persons with Alzheimer's disease and levels of depression among their family caregivers. *J Gerontol B Psychol Sci Soc Sci* 2001 Sep;56(5):301-313.

- (67) Elmstahl S, Ingvad B, Annerstedt L. Family caregiving in dementia: prediction of caregiver burden 12 months after relocation to group-living care. *Int Psychogeriatr* 1998 Jun;10(2):127-146.
- (68) Gallagher-Thompson D, Brooks JO, III, Bliwise D, Leader J, Yesavage JA. The relations among caregiver stress, "sundowning" symptoms, and cognitive decline in Alzheimer's disease. *J Am Geriatr Soc* 1992 Aug;40(8):807-810.
- (69) Grafstrom M, Winblad B. Family burden in the care of the demented and nondemented elderly--a longitudinal study. *Alzheimer Dis Assoc Disord* 1995;9(2):78-86.
- (70) Lim YM, Son GR, Song JA, Beattie E. Factors affecting burden of family caregivers of community-dwelling ambulatory elders with dementia in Korea. *Arch Psychiatr Nurs* 2008 Aug;22(4):226-234.
- (71) Reis MF, Gold DP, Andres D, Markiewicz D, Gauthier S. Personality traits as determinants of burden and health complaints in caregiving. *Int J Aging Hum Dev* 1994;39(3):257-271.
- (72) Robinson KM, Adkisson P, Weinrich S. Problem behaviour, caregiver reactions, and impact among caregivers of persons with Alzheimer's disease. *J Adv Nurs* 2001 Nov;36(4):573-582.
- (73) Asada T, Kinoshita T, Kakuma T. Analysis of behavioral disturbances among community-dwelling elderly with Alzheimer disease. *Alzheimer Dis Assoc Disord* 2000 Jul;14(3):160-167.
- (74) Tun SM, Murman DL, Colenda CC. Concurrent validity of neuropsychiatric subgroups on caregiver burden in Alzheimer disease patients. *Am J Geriatr Psychiatry* 2008 Jul;16(7):594-602.
- (75) Danhauer SC, McCann JJ, Gilley DW, Beckett LA, Bienias JL, Evans DA. Do behavioral disturbances in persons with Alzheimer's disease predict caregiver depression over time? *Psychol Aging* 2004 Mar;19(1):198-202.
- (76) Levesque L, Cossette S, Laurin L. A multidimensional examination of the psychological and social well-being of caregivers of a demented relative. *Research on Aging* 1995;17:332-360.
- (77) Craig D, Mirakhur A, Hart DJ, McIlroy SP, Passmore AP. A cross-sectional study of neuropsychiatric symptoms in 435 patients with Alzheimer's disease. *Am J Geriatr Psychiatry* 2005 Jun;13(6):460-468.
- (78) Eker E, Ertan T. Behavioral and psychological symptoms of dementia in eastern and southeastern Europe and the middle east. *Int Psychogeriatr* 2010;12(Suppl 1):409-413.

- (79) Savorani G, Vulcano V, Boni S, Sarti G, Ravaglia G. Behavioral disorders in dementia patients and their impact on the stress of caregiving relatives: The "ARAD" Questionnaire. *Arch* 1998;suppl 6:481-485.
- (80) Farran CJ, Keane-Hagerty E, Tatarowicz L, Scorza E. Dementia care-receiver needs and their impact on caregivers. *Clin Nurs Res* 1993 Feb;2(1):86-97.
- (81) Fuh JL, Liu CK, Mega MS, Wang SJ, Cummings JL. Behavioral disorders and caregivers' reaction in Taiwanese patients with Alzheimer's disease. *Int Psychogeriatr* 2001 Mar;13(1):121-128.
- (82) Hurt C, Bhattacharyya S, Burns A, et al. Patient and caregiver perspectives of quality of life in dementia: An investigation of the relationship to behavioural and psychological symptoms in dementia. *Dementia and Geriatric Cognitive Disorders* 2008;Vol.26(2):138-146.
- (83) Arriola E, Ignacio DJ, Antonio BJ, Gallego R. Open-label, observational study of the effects of risperidone on the behavioral and psychological symptoms of dementia and caregiver stress in the community setting. *Am J Geriatr Pharmacother* 2005 Mar;3(1):8-16.
- (84) Kaufer DI, Cummings JL, Christine D, et al. Assessing the impact of neuropsychiatric symptoms in Alzheimer's disease: the Neuropsychiatric Inventory Caregiver Distress Scale. *J Am Geriatr Soc* 1998 Feb;46(2):210-215.
- (85) Matsumoto N, Ikeda M, Fukuhara R, et al. Caregiver Burden Associated with Behavioral and Psychological Symptoms of Dementia in Elderly People in the Local Community. *Dementia and Geriatric Cognitive Disorders* 2007;Vol.23(4):219-224.
- (86) Meiland FJ, Kat MG, van TW, Jonker C, Drees RM. The emotional impact of psychiatric symptoms in dementia on partner caregivers: do caregiver, patient, and situation characteristics make a difference? *Alzheimer Dis Assoc Disord* 2005 Oct;19(4):195-201.
- (87) Neil W, Bowie P. Carer burden in dementia--assessing the impact of behavioural and psychological symptoms via self-report questionnaire. *Int J Geriatr Psychiatry* 2008 Jan;23(1):60-64.
- (88) Pang FC, Chow TW, Cummings JL, et al. Effect of neuropsychiatric symptoms of Alzheimer's disease on Chinese and American caregivers. *Int J Geriatr Psychiatry* 2002 Jan;17(1):29-34.
- (89) Rohde G, Quiroga P, Fasce M, Fasce F. Noncognitive symptoms in Alzheimer disease and caregivers distress in Chile. *Brain Cogn* 2002 Jul;49(2):253-255.
- (90) Tan LL, Wong HB, Allen H. The impact of neuropsychiatric symptoms of dementia on distress in family and professional caregivers in Singapore. *Int Psychogeriatr* 2005 Jun;17(2):253-263.

- (91) Mets T, Vandewoude M, Jacquy J, et al. Patient and caregiver outcomes after 6 +/- 1.5-months of rivastigmine therapy for mild-to-moderate Alzheimer's disease: the Belgian FExT study. *Curr Med Res Opin* 2007 Oct;23(10):2485-2501.
- (92) Scott A, Lewis D, Loughlin N. Dementia and challenging behaviour: the needs of family caregivers. *Nurs Older People* 2005 Mar;17(1):26-31.
- (93) Shin IS, Carter M, Masterman D, Fairbanks L, Cummings JL. Neuropsychiatric symptoms and quality of life in Alzheimer disease. *Am J Geriatr Psychiatry* 2005 Jun;13(6):469-474.
- (94) Rymer S, Salloway S, Norton L, Malloy P, Correia S, Monast D. Impaired awareness, behavior disturbance, and caregiver burden in Alzheimer disease. *Alzheimer Dis Assoc Disord* 2002 Oct;16(4):248-253.
- (95) Aalten P, de Vugt ME, Lousberg R, et al. Behavioral problems in dementia: a factor analysis of the neuropsychiatric inventory. *Dement Geriatr Cogn Disord* 2003;15(2):99-105.
- (96) Son J, Erno A, Shea DG, Femia EE, Zarit SH, Stephens MA. The caregiver stress process and health outcomes. *J Aging Health* 2007 Dec;19(6):871-887.
- (97) Goode KT, Haley WE, Roth DL, Ford GR. Predicting longitudinal changes in caregiver physical and mental health: a stress process model. *Health Psychol* 1998 Mar;17(2):190-198.
- (98) Chiu MJ, Chen TF, Yip PK, Hua MS, Tang LY. Behavioral and psychologic symptoms in different types of dementia. *J Formos Med Assoc* 2006 Jul;105(7):556-562.
- (99) Weiner B. An attributional theory of motivation and emotion. New York: Springer-Verlag, 1986.
- (100) Wadley VG, Haley WE. Diagnostic attributions versus labeling: impact of Alzheimer's disease and major depression diagnoses on emotions, beliefs, and helping intentions of family members. *J Gerontol B Psychol Sci Soc Sci* 2001 Jul;56(4):244-252.

Chapter 2:

The differential impact of unique behavioral and psychological symptoms for the dementia caregiver: How and why do patients' individual symptom clusters impact caregiver depressive symptoms?

Abstract

Although cognitive decline is considered the clinical hallmark of dementia, an extensive body of literature suggests that the non-cognitive, or behavioral and psychological symptoms associated with dementia (BPSD), are more burdensome to caregivers. BPSD consist of a wide variety of patient behaviors including depression, physical aggression and paranoid delusions. Yet it remains unclear whether specific symptoms have a differential impact on caregivers. The aims of this study were to assess how BPSD symptoms, categorized based on how they may affect caregivers, impact depressive symptoms for caregivers of patients with Alzheimer's Disease (AD) and Dementia with Lewy Bodies (DLB) and to test the pathways by which BPSD symptom clusters impact caregiver depressive symptoms. Using data from a longitudinal study of dementia patients and their caregivers, we analyzed the relationship between four BPSD symptom clusters (patient depressive symptoms, accusatory/aggressive behaviors, non-threatening psychotic symptoms, and difficult to manage behaviors) and caregiver depressive symptoms among 160 patient-caregiver dyads in up to 6 years of follow-up. Using multivariate GEE logistic models, we found small effects among all four clusters tested and caregiver depression (OR range=1.03-1.55), and that only the presence of patient depressive symptoms significantly impacted caregiver depression (OR=1.55; 95% CI=1.14-2.11). This relationship was mediated by both caregiver report of the symptom's impact on the patient and perceived burden to caregivers. These findings did not vary based on patient dementia diagnosis (DLB vs. AD). Given our findings, research in this field should further test the effects of individual BPSD symptoms and should also consider how symptoms may negatively impact caregivers by increasing burden and evoking empathy for the patient. Finally, future work in this area should

explore the timing and change in patient depressive symptoms and other individual BPSD as they relate to caregiver outcomes.

Introduction

As life expectancy increases in the United States (U.S.) and internationally, the aging population and the number of people living with chronic diseases such as dementia continues to grow.(1) Consequently, the number of family members providing informal (i.e., non-professional or family) caregiving to individuals with dementia has also increased.(2;3) While family caregivers provide a critical service to family members in lieu of more formal sources of long-term care support, they often suffer from chronic stress(4) which results in negative consequences for the caregiver's mental and physical health. In addition to causing undue suffering for caregivers, the maintenance of a healthy patient-caregiver dyad is beneficial for patients who most often prefer in-home care, and is financially imperative given current lack of public resources available for nursing home placement or paid caregiving.(5-7)

Although cognitive decline is considered the clinical hallmark of dementia, an extensive body of literature suggests that the non-cognitive, or the behavioral and psychological symptoms associated with dementia (BPSD) are more burdensome to caregivers and have greatest impact on decisions to institutionalize patients.(4;8-14) BPSD, which consist of a wide variety of patient behaviors including depression, physical aggression and paranoid delusions, are highly prevalent in patients with dementia over the course of their illness.(15-19) In a large population-based study of patients with dementia, 97% developed one or more symptoms over a five-year period.(20) Although BPSD consist of such wide-ranging symptoms, it remains unclear whether specific symptoms, or symptom clusters (distinguished based on clinical manifestations or on an empirical basis) differentially impact caregivers. The vast majority of research studies that have concluded that BPSD have a negative impact on caregivers have solely examined cumulative scores of BPSD.(11;21-24) By grouping together all BPSD as one construct, we cannot

determine whether there are individual symptoms/symptom clusters which are most stressful for caregivers, a potential missed opportunity to target interventions to better meet the clinical needs of patients and caregivers.

The limited research that differentiates individual symptoms is largely exploratory and does not simultaneously control for the impact of multiple BPSD(25-40). Furthermore, when differentiated, BPSD are categorized broadly based on the patient's clinical manifestations. While this system of categorization is appropriate for monitoring symptom progression and making appropriate treatment recommendations *for patients*, it fails to conceptualize BPSD from the perspective of their impact on *the caregiver*. Different types of symptoms may have differential impact on caregivers. Delusional or paranoid behaviors such as accusing the caregiver of plotting to leave her/him may be particularly disturbing to the caregiver who may take the behaviors personally. Similarly, aggressive behavior including physical violence cannot be easily dismissed by caregivers and may make the caregiver fearful of the patient and weaken the caregiver's commitment to ongoing at-home care. On the other hand, behaviors that are very difficult to manage, but not directed at the caregiver, e.g., wandering at night, may feel less threatening to the caregiver and result in fewer depressive symptoms. Patient depression has been repeatedly reported as a predictor of caregiver depression,(26-29;41;42) and may be particularly difficult to handle for the caregiver who perceives the patient as suffering.

Conceptual model

According to the stress process model,(21;43) caregiving is a chronic stressor that gives rise to strains from multiple domains and ultimately leads to increased risk for psychiatric distress and diagnosable disorder. The model differentiates between the objective, more concrete stressors

(e.g., BPSD, functional dependence or cognitive impairment), the caregiver's subjective experience (or appraisal) of those stressors, and background and contextual factors (e.g., education, living situation, age) which impact the stressor and caregiver outcomes (see Figure 2.1). The model delineates the mechanism by which objective stressors such as individual BPSD impact caregiver depressive symptoms. Using this model, various studies have reported that the association between objective stressors such as BPSD and mental and physical health outcomes of caregivers are mediated by subjective stress appraisal.(44-46) Indeed, caregiver interventions have decreased depression for caregivers by reducing negative appraisal of stressors without reducing the actual count of these stressors.(47)

While the stress process model has dominated research aimed at understanding negative mental health consequences for dementia caregivers by delineating the stress appraisal pathway, other pathways may be part of this process. Most recently, the importance of the role of patient suffering was proposed by Schulz and colleagues.(48) Suffering as a pathway by which BPSD may cause depression in caregivers gives weight to the patient's perspective, suggesting that perception of the patient's quality of life and their ability to function in day-to-day activities may affect the caregiver by evoking empathy for the patient.

Study Aims

Determining whether individual BPSD symptom clusters differentially impact caregiver outcomes and examining the mechanisms by which individual symptoms impact caregivers can help target intervention and prevention efforts for caregivers. The aims of this study are to assess how distinct BPSD symptoms, or symptom clusters, impact depressive symptoms for caregivers of patients with both Alzheimer's Disease (AD) and Dementia with Lewy Bodies

(DLB). We will specifically examine the relationship between caregiver depressive symptoms and four dementia patient symptom clusters: accusatory and aggressive symptoms, depressive symptoms, non-threatening psychotic behaviors, and difficult to manage behaviors. We hypothesize that while each behavior cluster will negatively impact caregivers, accusatory and aggressive behaviors will have a stronger relationship with caregiver depressive symptoms than other BPSD symptom clusters because they are difficult to ignore and may be perceived as more threatening to the caregiver. Additionally, we hypothesize that the relationship between BPSD symptom clusters and caregiver depressive symptoms are mediated by both caregiver perceived burden of behavior (i.e., perceived stress) and perceived impact of behavior on patient functioning (i.e., suffering).

Methods

Sample

In the Predictors 2 study, a cohort of patients with probable AD and DLB was followed prospectively from early stages of patient illness. Patients were recruited from memory disorder centers or private physician offices in three sites between 1997 and 2008: Columbia University College of Physicians and Surgeons; Johns Hopkins University School of Medicine; and Massachusetts General Hospital. The inclusion and exclusion criteria and evaluation procedures of the Predictors study have been fully described elsewhere.⁽⁴⁹⁾ Briefly, all patients were diagnosed in a consensus conference with at least two faculty physicians specializing in dementia and one faculty neuropsychologist. All AD patients met NINCDS-ADRDA criteria for probable AD⁽⁵⁰⁾ and intellectual impairment was documented with neuropsychological testing. At entry into study, each AD participant was required to have relatively mild dementia

operationalized as a modified Mini Mental State Examination (MMSE)(51) score ≥ 30 , equivalent to a score of ≥ 16 on the standard Folstein MMSE.(52) Patients with DLB were diagnosed according to the 1996 consensus guidelines for the disease.(53) Participants were also required to have at least one family member/informant available. Exclusion criteria were parkinsonism, stroke, alcoholism, schizophrenia, schizoaffective disorder, and electroconvulsive treatments.

During an initial visit, the following data were collected about the patient via clinical assessment: patient and caregiver demographic data, medical history, neurological evaluation, handedness, presenting features of cognitive impairment, functional status, family history of dementia, onset dating and features, and psychiatric history. Follow-up data were collected at 6-month intervals via inpatient visit thereafter until dropout or death including: neurological evaluation, functional and cognitive status, medical and psychiatric history, and quality of life. If patients were unable to travel to the outpatient clinic for evaluation, they were visited at their homes, nursing homes, or health care facilities. There is 94% follow up of patients. Patients who did not respond at a particular visit could respond at a subsequent visit. Autopsy data were also collected when possible to confirm diagnoses.

The Predictors Caregiver study was initiated in 2004. Detailed data on the mental health status of the informal caregivers of the patient cohort were collected for 160 patient-caregiver dyads. A total of 169 patients were active in the Predictors study at the time of, or subsequent to, the launching of the Caregiver study. Of these patients, six did not have an eligible informal caregiver to complete the study (3.6%). Of the 163 eligible patient-caregiver dyads, 98.2% have caregiver data available for at least one assessment. (Three caregivers refused to answer questions on their experiences as a caregiver). Because the main Predictors study was initiated

prior to the Caregiver study, patients had been in the study for different time periods when the Caregiver study was initiated. Baseline caregiver data were collected for 14.4% of dyads at patient baseline, 5% within the patient's first year of follow-up, 11.3% within the patient's second year of follow-up, 18.8% in the patients third year of follow-up, 23.8% in the patients fourth year of follow-up, and 15.6% in the patient's fifth year of follow up. Eleven percent of first caregiver assessments occurred after the patient was followed for at least five years. While the study is ongoing, this analysis includes data collected through August 2010 at which point 670 caregiver assessments were available. On average, each dyad completed 4.2 assessments (range=1-12).

Measures

Outcome measure

Caregiver depressive symptoms was measured by the six-item depression subsection of the brief symptom inventory (BSI).(54) Caregivers were asked how much during the past week they were bothered by the following: feeling lonely, feeling blue, feeling no interest in things, feeling hopeless about the future, feelings of worthlessness, and thoughts of ending your life using a five-point Likert scale response for each item ranging from "not at all" to "extremely". A higher score indicates higher depressive symptoms. The mean score across six symptoms was calculated (mean=1.44, standard deviation (SD) =0.56). The standardized Chronbach's coefficient alpha was >.80 indicating acceptable reliability.(55) For use in logistic regression analysis, mean BSI score was dichotomized as no depressive symptoms (<2) and depressive symptoms (>=2). Caregivers categorized as having depressive symptoms were (1) one SD above

the mean depressive symptom score and (2) indicated that on average each of the six symptoms bothered or impacted them from a minimal to extreme level.

Exposure measures

The Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD)(56) was used to measure patient BPSD at baseline and at subsequent 6 month intervals. The CUSPAD (see Appendix 2.A) is a semi-structured rating scale that a clinician or research assistant administers to the informant regarding the presence of 26 patient symptoms during the last month before each interview. Interrater reliabilities for individual symptoms range from kappa coefficients of .61-.73.(56) Existing clinical grouping of symptom clusters in the CUSPAD were not maintained nor did we empirically determine how symptoms were clustered within the patient as the study aim was not patient-centered (e.g., to determine varying etiologies of BPSD syndromes among patients or to assess patient treatment options). Instead, we created four non-overlapping symptom clusters based on a review of the literature and the hypothesized differential impact of symptom clusters on caregivers.

1. Accusatory and aggressive symptoms were measured based on the following six CUSPAD items designed to measure paranoid and abandonment delusions as well as aggression: beliefs that people are stealing things, beliefs that they have an unfaithful wife/husband, other unfounded suspicions, accusing caregiver of plotting to leave him/her, engaging in threatening behavior, and engaging in physical violence. Given that these behaviors may be directed at the caregivers and are unlikely to be easily ignored, they may be particularly disturbing to the caregivers. We constructed a dichotomous variable to characterize the presence or absence of one or more accusatory and aggressive symptoms (see Appendix 2.B).

2. *Non-threatening psychotic symptoms* consisted of the following 13 items which constitute the remainder of the psychotic symptoms (hallucinations, illusions, misidentification delusions and somatic delusions) measured in the CUSPAD: belief that the patient has cancer or other physical illness, belief that people are in the house when nobody is there, belief that someone else is in the mirror, belief that the spouse/caregiver is an imposter, belief that the patient's house is not his/her home, belief that the characters on television are real, report that one thing is something else, hearing voices when no one is there, seeing visions; reporting unusual smells, and other reports of false beliefs or strange ideas or hallucinations. These items are categorized as non-threatening because while they are by definition psychotic, and likely disturbing to the caregiver because they are non-normative, they are not directly threatening the caregiver. We constructed a dichotomous variable to characterize the presence or absence of any non-threatening psychotic symptoms (see Appendix 2.B).

3. *Depressive symptoms*: Patient depressive symptoms were defined as having (1) depressed mood and (2) either difficulty sleeping or change in appetite. We constructed a dichotomous variable indicating the presence or absence of patient depressive symptoms (see Appendix 2.B).

4. *Difficult to manage behaviors*: Difficult to manage behaviors was dichotomized to indicate the presence or absence of one or more of the following four behaviors: wandering away from home or from the caregiver, showing agitation or restlessness, making verbal outbursts, and sundowning (increased disorientation, restlessness, agitation in the late afternoon or evening) (see Appendix 2.B).

Potential confounding variables

Because our main focus was on the relationship between BPSD and caregiver depressive symptoms, we examined a variety of (1) non-BPSD objective stressors and (2) background and contextual variables as potential confounding variables.

Objective stressors

Patient cognitive status was assessed at each visit using the MMSE(52) in which a higher MMSE score indicates better cognitive status. Patient functional status was assessed at each visit using parts I and II of the Blessed Dementia Rating Scale (BDRS).(57) Part I measures instrumental activities of daily living (IADL) (i.e., shopping, housekeeping) and has a maximum score of eight, indicating the lowest level of function. Part II measures basic activities of daily living (ADL) (i.e., eating, dressing, and toileting) and has a maximum score of nine. Patient level of dependence was assessed using the Dependence Scale.(58) The scale is based on informant interviews, specifically targeting the informant's impression of the amount of assistance required by the patient in everyday tasks. The total score has a maximum of 15, indicating the highest degree of dependency. The scale includes an assessment of equivalent institutional care the patient requires (regardless of their actual status) divided into: limited home care (independent living requiring some assistance), adult home (living in a supervised setting), and health-related facility (requiring round-the-clock supervision of care). Patients' medical histories were used to construct a modified version of the Charlson index of comorbidity.(59) Comorbidities included myocardial infarction, congestive heart failure, peripheral vascular disease, hypertension, chronic obstructive pulmonary disease, arthritis, gastrointestinal diseases, mild liver disease, diabetes, chronic renal disease, and systemic malignancy. (First available diagnosis was used for <4% baseline assessments given lack of variability of comorbidity index over study period.) A modified Unified Parkinson's Disease Rating Scale(60;61) was administered at each visit to

measure the presence or absence of extrapyramidal signs (EPS)(e.g., tremors, rigidity).

Following previous work,(62) a dichotomous indicator was constructed for the use of EPS if any of the following 11 items were rated 2 or higher (0 being normal and 4 indicating maximum impairment): speech, facial expression, tremor at rest, neck rigidity, right arm rigidity, left arm rigidity, right leg rigidity, left leg rigidity, posture, gait, and bradykinesia).

Background and contextual factors

Patient age, ethnicity, sex, and highest level of education were recorded at the baseline visit; marital status was recorded at each visit. Whether or not the patient had a home health aide was recorded annually. Duration of illness in years was estimated by a neurologist based on baseline interviews with the patient and caregiver.

Caregiver age, gender, ethnicity, highest level of education, and relationship to patient were recorded at the start of the Caregiver study. Whether the caregiver lives with the patient, frequency of contact with patient, and length of time caregiver has known patient were recorded at each visit. Whether caregiver assists with basic and instrumental activities of daily living, the amount of hours the patient spends per day with the caregiver, whether a home health aide/home attendant assisted with care, and caregiver's employment status were reported annually. We imputed missing data for six month (or semi-annual) intervals by using subsequent visit annual caregiver data scores when available. By imputing data using the subsequent six month visit, this approach overestimates the patient's reliance on caregivers as, in general, more services are provided as patient functional status declines over time.

Mediator variables

Symptom-specific perceived burden to caregiver or subjective stress was measured by asking the caregiver the following after the presence of a symptom/cluster of behaviors was reported, “How difficult or disturbing do you find these behaviors to manage or deal with?” Response options based on a five-point Likert scale ranging from no difficulty to extreme difficulty were dichotomized as not difficult (no difficulty, minimal or mild) and difficult (moderate to severe difficulty). Similar single item measures of burden have been validated for screening burden.⁽⁶³⁾ Patient impact was measured based on caregiver response to the following question: “To what extent would you say these behaviors have affected the patient’s daily activities and functioning?” Response options based on a five-point Likert scale were dichotomized as no effect (no effect, minimal or mild) and affected patient (moderate to severe difficulty). If a patient symptom was reported to be not present, and the caregiver was therefore not asked any subsequent questions on the impact of the behavior, perceived impact and patient impact of behavior was coded as “no effect”.

Analysis

We examined the simultaneous association between patient BPSD and caregiver depressive symptoms at any given time point for all patient-caregiver dyads. Multiple time points nested within the patient-caregiver dyad were included in analyses to test the association between BPSD symptom clusters and caregiver depressive symptoms using all available data. To account for repeated observations within dyads, we employed a generalized estimating equation (GEE) extension of the logistic regression using an exchangeable correlation structure with a robust standard error estimator. Listwise deletion was used in analyses, i.e., individuals with missing data on any of the covariates were excluded from regression models (<5%). We conducted unadjusted analyses to examine the association between each symptom cluster and caregiver

depression and multivariate models that simultaneously tested each symptom cluster while controlling for confounders. Subsequent models were tested to control for the impact of patient anti-depressant and neuroleptic use on the BPSD-caregiver depression relationship. The same analysis was also conducted treating the outcome variable as a continuous variable using GEE extension of Poisson regression analysis.

To determine which variables would be included in the final model, bivariate associations between (1) caregiver depressive symptoms and potential confounders and (2) individual BPSD and potential confounders were assessed. Unadjusted logistic regression models were used to determine bivariate associations using multiple time points per dyad as well as at first caregiver assessment only. Because of sample size limitations only those variables that showed a statistically significant effect on the outcome at the 0.10 level, were associated with at least one symptom cluster, and were not highly correlated with other variables (correlation $>.5$) in the bivariate analysis were included in the final adjusted logistic regression model.

Mediation analyses were restricted to symptom clusters that had statistically significant impact on the main exposure outcome ($p < .05$). We used techniques outlined by Baron & Kenny(64) to test for mediation. First, we examined the unadjusted relationship between two mediator variables (patient impact and burden to caregiver) and caregiver depression using logistic regression GEE models. Next, we examined the unadjusted relationship between BPSD symptom clusters and each mediator using chi-square analysis. Finally, we looked at the effect of each mediator on the relationship between individual symptom clusters and caregiver depression in full GEE logistic models. We compared beta estimates derived from logistic models for the role of symptom clusters in individual adjusted models that controlled for mediation to models that did not control for the effect of a mediator.

GEE models were fit using PROC GENMOD in SAS. All analyses were completed using SAS version 9.2.

Results

Characteristics of patients and their caregivers

Baseline descriptive and clinical characteristics of the study sample are depicted in Table 2.1.

Mean patient age was 75.4 years, slightly more than half were female, and most were white. The vast majority (92%) had at least a High School education and almost two thirds were married.

The majority of patients suffered from AD (86.3%). Consistent with study enrollment criteria, patients were at early stages of illness with relatively mild cognitive impairment and average neurologists' estimate of illness duration was 4.8 years. Average dependence score was 5.0 and functional status score was 3.7 indicating a mild level of dependence and high physical function. Accordingly, very few patients lived in a nursing home (3.8%) and only 12% required any home health care assistance. More than half of patients did not have any comorbid conditions and only 17.2% exhibited EPS.

Caregiver characteristics at time of first caregiver assessment are summarized in Table 2.2.

Caregivers were on average 65 years old, female (76%), predominantly white, highly educated, and just less than half worked outside of the home. More than half of caregivers (55%) were spouses of patients and 36.3% were children of patients. The vast majority (89%) lived with the patient and reported being very involved with patient activities. Almost 40% spent more than 12 hours daily with the patient and 44.9% reported assisting patients daily with basic activities (e.g., eating, dressing, bathing). The majority reported assisting patients daily with tasks such as shopping, transportation, and chores.

Prevalence of BPSD symptom clusters

As summarized in Table 2.3, BPSD of any kind were common at baseline (57.96%) and were almost universally reported by the end of the study period (93.13%). Each of the four patient symptom clusters were common at patient baseline with depression least common (17.95%) and difficult behaviors the most frequently reported (41.94%). All four individual BPSD clusters were more commonly reported among caregivers with depressive symptoms compared to those caregivers with no depressive symptoms across multiple time points per patients (see Table 2.4 for descriptive comparison).

Association between symptom clusters and caregiver depressive symptoms

We used logistic GEE analysis to examine the impact of each of the four symptom clusters on caregiver depression (1) unadjusted, (2) after simultaneously adjusting for all other symptom clusters, and (3) after simultaneously controlling for all relevant confounders and symptom clusters (Table 2.5). In our final model, each cluster had a positive, yet weak association with caregiver depression, with patient depressive symptoms showing the strongest effect (OR=1.55) and patient difficult behaviors having the weakest effect (OR=1.03). Only patient depressive symptoms had a statistically significant ($p<.05$) impact on the likelihood of caregiver depression (OR=1.55; 95% CI=1.14-2.11), although non-threatening psychotic symptoms had borderline significance in the fully adjusted model (OR=1.39; 95% CI=.93-2.08). We also controlled for patient antidepressant and neuroleptic use (see Appendix 2.C) and found that the effect of patient depressive symptoms on caregiver depression remained of highest magnitude and statistically significant (OR=1.76; 95% CI=1.26-2.45) while all other symptoms clusters had 95% confidence intervals including the null.

Because the magnitude of effects among symptom clusters were all positive and in relatively close range, we further examined these relationships in subsequent models. First, we treated the outcome variable, depressive symptoms, as a continuous outcome using GEE Poisson regression analysis (see Appendix 2.D). These analyses confirmed our findings regarding the stronger predictive role of patient depressive symptoms after simultaneously adjusting for other symptom clusters. Similarly, we also replicated our findings using continuous measures of each BPSD cluster, e.g., the more non-threatening psychotic symptoms the patient exhibited, the higher the BPSD score (see Appendix 2.E). When considering symptom count as a measure of symptom severity, our findings continued to suggest that patient depression has the largest effect, and remained the only statistically significant ($p < .05$) predictor of caregiver depression.

Although the estimate for patient depressive symptoms was statistically significant while the other clusters were not, this does not necessarily imply that the estimates were significantly different from each other. In order to explicitly test whether the effects of patient depression symptoms were significantly different than the effects of other BPSD symptom clusters on caregiver depression, we compared logistic regression models in which the parameter estimates for patient depression and each of the other symptom clusters are forced to be equal against a model where patient depression is allowed to differ. Using methods described by Rindskopf(65) we found that the two models were significantly different ($p < .05$) by comparing differences in the likelihood ratio chi-square statistics for the restricted and unrestricted models (see Appendix 2.F). Furthermore, the observed differential effect of patient depressive symptoms was not accounted for by correlations between individual BPSD (range=0.12-0.28) (see Appendix 2.G).

Mediation

Using mediation analyses, we confirmed the role of both patient impact and perceived burden to caregivers as mediators of the patient depression and caregiver depression relationship. Both of the mediators tested, patient impact and perceived burden to caregiver, were significantly associated with caregiver depressive symptoms. Those caregivers who reported that patient depressive symptoms severely impacted patients were 1.96 times as likely as those who did not report that patient symptoms impacted patients to have depressive symptoms (95% CI=1.12-3.42). Those caregivers who reported that patient depressive symptoms were difficult to handle were 2.63 times as likely as those who did not report such difficulty to have depressive symptoms (95% CI=1.41-4.90). We also found that patient depressive symptoms were significantly associated with caregivers reporting that patient depressive symptoms were difficult to handle and that they impacted patients ($p<.001$). In separate multivariate models, each mediator reduced the effect estimate of patient depressive symptoms on caregiver depressive symptoms (Table 2.6). Patient impact resulted in an 81% reduction in beta whereas burden resulted in a 90% reduction in the effect estimate of patient depressive symptoms. After controlling for either mediator, the effect of patient depression was no longer a significant predictor of caregiver depressive symptoms. Because of high correlation ($r=0.67$, $p<.01$) between impact on patient and perceived burden to caregiver, the joint effect of the two mediators could not be tested in one model.

Post-hoc analyses of psychotic symptoms

Given that the non-threatening and aggressive psychotic symptoms appeared to have a small, although non-significant ($p<.05$) effect on caregiver depression, and because of previously documented associations between psychotic symptoms and caregiver depression,(27;41) we conducted several post-hoc analyses to examine the relationship between psychotic symptoms

and caregiver depression in this study sample. First, we tested whether accusatory symptoms and aggressive symptoms individually impacted caregiver depression; we continued to find no relationship when this symptom cluster was further divided in a fully adjusted model. We also attempted to determine whether any one psychotic symptom in particular appeared to be overwhelmingly driving the relation between non-threatening psychotic symptoms and caregiver depression but did not find this to exist. We next re-categorized psychotic symptoms based on their clinical classifications as hallucinations and delusions (because illusions were only reported by <3% of patients they were not included) to determine how they impact caregiver depression. In a multivariate model controlling for patient depressive symptoms, whether the caregiver is the patient's spouse and patient functional status, hallucinations remained unimportant, although delusions retained statistical significance (OR=1.50; 95% CI=1.02-2.19). When we examined the relationship between the presence of any type of patient psychotic symptom and caregiver depression in a multivariate analysis controlling for other non-psychotic symptom clusters and covariates, psychotic symptoms as a whole were significant (OR=1.59; 95% CI=1.08-2.37). (See Appendix 2.H for details on post-hoc analysis of patient psychotic symptoms and caregiver depression.)

Discussion

BPSD are highly prevalent among patients with dementia over the course of disease.

Differentiating which types of symptoms are most problematic for caregivers can help to target BPSD treatment efforts and inform caregiver intervention studies. In this study we hypothesized that accusatory and aggressive symptoms (e.g., threatening behavior, unfounded suspicions) would result in the most depressive symptoms for caregivers. While accusatory and aggressive symptoms as well as non-threatening psychotic symptoms exhibited small positive effects on

caregiver depression, they were not statistically significant after controlling for other symptoms and confounders. Instead, we consistently found that, patient depressive symptoms had a greater magnitude of effect on caregiver depression that remained statistically significant.

The finding that patient depressive symptoms is associated with increased caregiver depression is supported in the literature, (26-29;41;42) although studies often failed to simultaneously control for the impact of other possible BPSD and important confounders. For example, while Neundorfer et al (29) found that over five years increase in patient depressive symptoms predicted increase in caregiver depressive symptoms, the study did not consider the role of patient symptoms other than depression that may have changed over time and influenced caregiver outcomes. The potential for a negative effect of depression above and beyond other BPSD on caregivers is especially important given that depression is highly prevalent among patients with AD with estimates ranging up to 40%.(66;67) Furthermore, pharmacological treatment efforts for depression in dementia, although common, remain complicated due to issues with polypharmacy and difficulty assessing symptom change in patients due to cognitive impairment.(68)

Depression may be especially challenging for caregivers to handle not only due to the difficulty it causes caregivers in dealing with the patients, but also because of the negative impact it has on the patient's quality of life.(69;70) In our examination of mediators of the patient depression-caregiver depression relationship we found that both impact on patient's functioning as well as burden to caregiver played an important role. While caregiver burden has been previously shown to mediate the relationship between patient objective behavior and caregiver outcomes,(44-46) the role of impact on patient functioning in the causal pathway has not previously been explored. Our findings suggest that caregivers recognize the difficulty that

patient depressive symptoms may cause for patients and that this mechanism may independently result in negative caregiver outcomes such as depression. This novel understanding of the importance of the patient experience as a mediator of the BPSD-caregiver depression relationship, similar to research that has examined the patient suffering pathway,(71;72) suggests we may need to take a new approach for caregiver intervention. Specifically, in addition to focusing on respite care or skills training for caregivers, interventions can minimize impact of symptoms for the patient, thus helping the caregiver to cope with the effects of the symptoms and suffering experience of the patient.

Our lack of strong positive findings surrounding the association between accusatory and aggressive symptoms and caregiver depressive symptoms was unexpected. We hypothesized that these symptoms would be most challenging as they represent aberrant behavior (because of their psychotic nature) and are difficult to ignore because they are largely directed at the caregiver (e.g., accusations of infidelity). While caregiver depressive symptoms may not be significantly impacted by such symptoms, other outcomes such as caregiver burden or desire for institutionalization could be impacted by these types of symptoms, and these relationships should be explored further. Future research should continue to examine which elements of psychotic symptoms are most disturbing to caregivers, especially given the trend for these symptom clusters to impact caregiver depression in this study. Larger samples may be necessary to tease apart the differential effects of individual psychotic features on caregiver symptoms.

Most studies that examine caregiver outcomes such as depression are often limited to caregiver report of all aspects of patient activity and performance. In this study we were able to examine the association of caregiver depression with a wealth of clinical variables using validated clinician-administered scales including EPS, cognitive status, functional status and the presence

of other medical comorbidities. Patients had clinician-confirmed diagnosis of AD or DLB and we also examined the impact of neurologist estimated length of time with illness in the BPSD-caregiver depression relationship. We tested to see whether these variables and various detailed aspects of the patient-caregiver relationship (e.g., whether patient and caregiver lived together, amount of time spent daily together, and demographic characteristics) were associated with caregiver depression. In this sample the only clinical features of patient dementia illness that consistently impacted caregiver depressive symptoms were functional status and the presence of patient depressive symptoms. To our knowledge, this is the first study to report these findings and to systematically examine detailed clinical features of dementia illness using validated scales used for clinical assessments.

Among patients with AD and DLB followed up to six years, 43% experienced depressive symptoms. Our findings suggest that these highly prevalent patient depressive symptoms are associated with caregiver depressive symptoms across any time point in the patient-caregiver relationship. Future research should begin to examine the effect of the timing of individual patient symptoms and their trajectories on caregiver outcomes. Establishing how timing of depressive (and other individual) symptoms impacts caregiver response is paramount to understanding the etiology of caregiver depression and developing effective interventions appropriate to the changing course of disease. As patient-caregiver relationships will likely extend as new treatments develop to slow the progression of dementia, studies that examine caregiver response to BPSD should make use of longitudinal designs to consider the role of timing and adaptation on behavior. For example, challenges that occur early in the caregiving career may have lasting impact over the course of the patient's illness and should be explored. While we did not find strong relationships between other types of BPSD and caregiver

depression at any time point in the patient-caregiver relationship, it is possible that if we examine the impact of BPSD (e.g., accusatory/aggressive symptoms) at specific stages of the patient-caregiver relationship, we may determine that associations indeed exist.

The experience of symptoms in AD vs. DLB

The study sampled included patients with AD and DLB. While the core BPSD symptoms may be similar, and indeed, assessed with the same instruments, dementias of different etiologies are characterized by varied prevalence and trajectories of behavior symptoms.(73;74) Yet little is known about caregivers' reactions to behavioral problems between diagnostic groups. Etiology of dementia, or diagnostic context, may influence the way that caregivers experience BPSD. According to attribution theory, perceptions of controllability of behaviors influence the emotional reaction of caregivers.(75) Diagnostic context may therefore play a role in explaining the relationship between BPSD and caregiver depression such that those caregivers who attribute more behaviors to disease are less likely to experience negative outcomes. Thus, psychotic behaviors which are considered characteristic of DLB and are more consistent throughout the course of illness may be viewed by that group of caregivers as more biological in nature and will be less associated with caregiver depression. While we originally planned to test whether the effects of BPSD were different for those patients with AD compared to those with DLB, the few number of cases with DLB (n=22) prevented our ability to test this interaction. While we did not find an effect of diagnosis on caregiver depression, and our results remained unchanged when we examined patients with AD only (see Appendix 2.I), future studies with larger samples should explore the role of dementia subtype diagnosis when examining BPSD-caregiver depression relationships.

Limitations

This study does have several limitations of note. Data were only available on 160 patient-caregiver dyads. While we had sufficient power to detect effect estimates of at least 2.0 between symptom clusters and caregiver depression, we may not have had sufficient power to detect more subtle differences between symptoms clusters after controlling for the effects of other symptoms. Furthermore, as in almost all studies of BPSD, this study relies on caregiver report of BPSD, which may itself be affected by the caregiver's mental health status. Given the cross-sectional nature of these data, we cannot rule out the possibility that caregiver depression itself impacted report of patient depressive symptoms. While the caregiving study was initiated when patients were at various stages of illness, we were able to test the effects of length of time with illness and cognitive status which had no effect on caregiver depression outcomes.

Measurement of patient depressive symptoms in this study must also be considered. Depression is difficult to recognize in dementia patients due to the overlapping nature of depressive symptoms with dementia and the inherent nature of cognitive impairment. Caregiver reports of patients' depression is especially challenging among those with advanced stages of illness, and is known to be underreported by caregivers regardless of their depression status.⁽⁷⁶⁾ Such non-differential underreporting of depression by all caregivers, suggests that the true association between patient depression and caregiver depression may be even stronger than we have concluded. Additionally, while the study used validated measures for caregiver and patient depressive symptoms, this study did not incorporate measures of depressive disorder, which may be of greater concern to clinicians. Furthermore, while we attempted to examine the effects of severity of patient BPSD on caregiver outcomes in post-hoc analyses by looking at a summary measure of number of symptoms exhibited, we were unable to look at the impact of individual

symptom frequency or severity based on symptom type and persistence. Future research should examine whether severity and frequency of BPSD, in particular, patient depression, impacts caregiver outcomes, while simultaneously examining other BPSD.

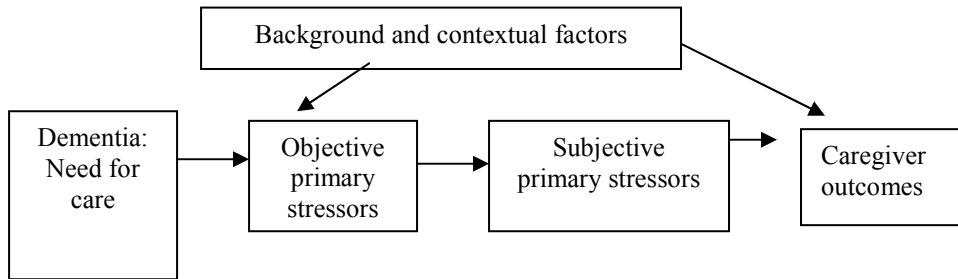
We also relied on single item measures of caregiver symptom-specific burden and patient impact that have not been validated. Future research should validate these measures and consider the development of more extensive scales to measure patient impact, in particular, given that no other assessments exist for this measure. Finally, this clinic sample of predominantly white patients with dementia may not be generalizable to all patient-caregiver dyads that exist in the population. The experience of patients' depression by caregivers from other racial/ethnic backgrounds may be very different.

Conclusion

While this study fails to find that one symptom cluster overwhelmingly negatively impacts caregivers above and beyond all others, our findings suggest that symptom clusters may not impact caregivers uniformly. While the presence of accusatory and aggressive behaviors as well as non-threatening psychotic behaviors in patients tend to negatively impact caregivers, patient depressive symptoms may have the most consistently negative impact on caregivers and may be driving research findings that suggest that BPSD impact caregiver depression. Given the high prevalence of BPSD among patients with dementia, it may be more useful for clinicians and researchers to continue to consider the effect of specific symptoms on caregivers, rather than focusing on the cumulative effect of a wide-range of behaviors. For example, effective behavioral therapies have been developed to specifically control depressive symptoms in patients with dementia.(77;78) Many of these psychosocial interventions involve caregivers in order to

directly alleviate symptoms for patients while simultaneously helping caregivers deal with management of the symptoms (e.g., via education, use of support groups).(79) Future studies should also begin to examine how timing of individual symptoms such as patient depression affects caregivers and how the stress of the symptoms and its effects change over time. These findings will lay foundations for treatment and intervention planning toward the ultimate goal of improving the mental health of the growing population of caregivers of patients with dementia in the U.S. and globally.

Figure 2.1: Diagram of stress process model



Adapted from: Pearlin LI, Mullan JT, Semple SJ, Skaff MM. (43)

Table 2.1: Patient characteristics at baseline (n=160)

Characteristic	Categories	Percent/ mean± SD
Age	mean ± SD	75.4 ± 7.4
Gender	Female	54.4%
Ethnicity	White Other	90% 10%
Years of schooling	mean ± SD Less than High School High School Above High School	14.7 ± 3.1 8.1% 26.3% 65.6%
Marital status	Married Widowed Other	63.1% 28.1% 8.8%
Living status	Home Retirement home Nursing home	89.4% 6.9% 3.8%
Site	Columbia University Johns Hopkins Mass General	44.4% 29.4% 26.3%
Diagnosis	Alzheimer's Disease Dementia with Lewy Bodies	86.3% 13.7%
Neurologist estimation of duration of illness in years	mean ± SD (range 1-18)	4.8 ± 2.5
Mini-mental state examination (MMSE) score	mean ± SD (range 9-30)	22.7 ± 3.7
Blessed functional activity scale score	mean ± SD (range 0-13)	3.7 ± 2.3
Total dependence	mean ± SD (range 0-12)	5.0 ± 2.4
Home health aide in last 3 months	Yes	11.9%
Modified comorbidity index	0 ≥1	51.6% 48.4%
Extrapyramidal signs	Yes	17.2%

SD=standard deviation

Table 2.2: Caregiver characteristics at initial caregiver assessment (n=160)

Characteristic	Categories	Percent or mean± SD
Age	mean ± SD	65.3 ± 14.4
Gender	Female	76%
Ethnicity	White Other	91% 9%
Years of schooling	mean ± SD Less than High School High School Above High School	15.8 ± 3.3 5.0% 18.4% 76.6%
Work at least part-time for pay	Yes	44.7%
Relationship to patient	Spouse Child Other relative/friend	55% 36.3% 8.7%
Years caregiver has known patient	mean ± SD (range 10-91)	49.6 ± 12.9
Lives with patient	Yes	89.4%
Time spent daily with patient	None Up to 3 hrs 3 to 5 hrs 6 to 9 hrs 9 to 12 hrs More than 12 hrs	2% 29.4% 11.8% 9.8% 8.5% 38.6%
Assists patient with ADLs	Yes	44.9%
Time spent daily assisting with IADLs	None Up to 3 hrs 3 to 5 hrs 6 to 9 hrs 9 to 12 hrs More than 12 hrs	18.9% 52% 20.3% 4.1% 1.4% 3.4%

SD=standard deviation; ADLs=Activities of daily living and include bathing, eating;
IADLS=Instrumental activities of daily living and include shopping, housekeeping

Table 2.3: Proportion of patients experiencing symptom clusters (n=160)

	Prevalence at patient baseline	Study period prevalence
Patient depressive symptoms, %	17.95%	43.13%
Patient accusatory/aggressive, %	22.58%	47.50%
Patient non-threatening psychotic behavior, %	24.84%	61.88%
Patient difficult behaviors, %	41.94%	85.00%
Any symptom cluster	57.96%	93.13%

Table 2.4: The prevalence of patient symptom clusters by caregiver depression status*

	All	Caregiver has depressive symptoms	Caregiver has no depressive symptoms
Patient depressive symptoms, %	20.21%	31.43%	18.07%
Patient accusatory/aggressive, %	23.73%	34.62%	21.65%
Patient non-threatening psychotic behavior, %	35.99%	49.52%	33.39%
Patient difficult behaviors, %	57.52%	64.76%	56.12%

*includes multiple assessments (mean = 4.2) per 160 patient-caregiver dyads

Table 2.5: Associations between symptom clusters and caregiver depression (n=160)*

	Model 1**		Model 2***		Model 3****	
	OR	95% CI	OR	95% CI	OR	95% CI
Depressive symptoms	1.77	1.28-2.44	1.58	1.15-2.17	1.55	1.14-2.11
Accusatory/aggressive behavior	1.42	0.99-2.01	1.15	0.79-1.68	1.17	0.82-1.69
Non-threatening psychotic behavior	1.76	1.22-2.53	1.59	1.07-2.37	1.39	0.93-2.08
Difficult behaviors	1.28	0.85-1.94	1.10	0.72-1.70	1.03	0.67-1.58

*includes multiple assessments (mean = 4.2) per 160 patient-caregiver dyads

**unadjusted

***adjusted for other patient symptom clusters

****simultaneously adjusted for other patient symptom clusters, patient functional status, whether caregiver is the spouse

Table 2.6: The mediating effect of patient impact and perceived caregiver burden on the association between patient depressive symptoms and caregiver depression (n=160)*

	Model 1		Model 2		Model 3	
	OR	95% CI	OR	95% CI	OR	95% CI
Patient depressive symptoms	1.56	1.14-2.13	1.09	0.71- 1.69	1.04	0.67-1.63
Spousal relationship	2.22	1.24-3.97	2.22	1.27- 3.90	2.18	1.22-3.90
Patient functional status	1.07	1.01-1.12	1.06	1.01- 1.11	1.06	1.02-1.12
Patient aggression	1.18	0.83-1.68	1.14	0.81- 1.60	1.09	0.76-1.57
Patient non-threatening behavior	1.40	0.94-2.07	1.46	0.98- 2.17	1.37	0.92-2.05
<u>Mediator 1: patient impact</u>	-----	-----	2.05	1.24- 3.39	-----	-----
<u>Mediator 2: perceived caregiver burden</u>	-----	-----	-----	----- ---	2.12	1.22-3.67

*includes multiple assessments (mean = 4.2) per 160 patient-caregiver dyads

References

- (1) 2009 Alzheimer's disease facts and figures. *Alzheimers Dement* 2009 May;5:234-270.
- (2) National Alliance for Caregiving, AARP. Caregiving in the U.S. Washington, DC: AARP; 2004.
- (3) Alzheimer's Association and National Alliance for Caregiving. Families care: Alzheimer's disease caregiving in the United States, 2004. 2004.
- (4) Schulz R, O'Brien AT, Bookwala J, Fleissner K. Psychiatric and physical morbidity effects of dementia caregiving: prevalence, correlates, and causes. *Gerontologist* 1995 Dec;35:771-791.
- (5) Arno PS, Levine C, Memmott MM. The economic value of informal caregiving. *Health Aff (Millwood)* 1999 Mar;18:182-188.
- (6) Gibson MJ, Houser A. Valuing the invaluable: a new look at the economic value of family caregiving. *Issue Brief (Public Policy Inst (Am Assoc Retired Pers))* 2007 Jun;1-12.
- (7) Langa KM, Chernew ME, Kabeto MU, et al. National estimates of the quantity and cost of informal caregiving for the elderly with dementia. *J Gen Intern Med* 2001 Nov;16:770-778.
- (8) Black W, Almeida OP. A systematic review of the association between the Behavioral and Psychological Symptoms of Dementia and burden of care. *Int Psychogeriatr* 2004 Sep;16:295-315.
- (9) Pinquart M, Sorensen S. Associations of stressors and uplifts of caregiving with caregiver burden and depressive mood: a meta-analysis. *J Gerontol B Psychol Sci Soc Sci* 2003 Mar;58:112-128.
- (10) Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. *Gerontologist* 1980 Dec;20:649-655.
- (11) Clyburn LD, Stones MJ, Hadjistavropoulos T, Tuokko H. Predicting caregiver burden and depression in Alzheimer's disease. *J Gerontol B Psychol Sci Soc Sci* 2000 Jan;55:S2-13.
- (12) Meshefedjian G, McCusker J, Bellavance F, Baumgarten M. Factors associated with symptoms of depression among informal caregivers of demented elders in the community. *The Gerontologist* 1998 Apr;Vol.38:247-253.
- (13) Ballard C, Lowery K, Powell I, O'Brien J, James I. Impact of behavioral and psychological symptoms of dementia on caregivers. *International Psychogeriatrics* 2000;Vol.12:93-105.

- (14) Donaldson C, Tarrier N, Burns A. The impact of the symptoms of dementia on caregivers. *Br J Psychiatry* 1997 Jan;170:62-68.
- (15) Steinberg M, Lyketsos CG. Psychiatric disorders in people with dementia. In Weiner, Myron F (Ed); Lipton, Anne M (Ed). *The American Psychiatric Publishing textbook of Alzheimer disease and other dementias*. (pp. 263-281). Arlington, VA, US: American Psychiatric Publishing, Inc. 2009.
- (16) Steinberg M, Sheppard JM, Tschanz JT, et al. The incidence of mental and behavioral disturbances in dementia: the Cache County study. *J Neuropsychiatry Clin Neurosci* 2003;15:340-345.
- (17) Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *JAMA* 2002 Sep 25;288:1475-1483.
- (18) Aalten P, de Vugt ME, Jaspers N, Jolles J, Verhey FR. The course of neuropsychiatric symptoms in dementia. Part I: findings from the two-year longitudinal Maasbed study. *Int J Geriatr Psychiatry* 2005 Jun;20:523-530.
- (19) Sink KM, Covinsky KE, Newcomer R, Yaffe K. Ethnic differences in the prevalence and pattern of dementia-related behaviors. *J Am Geriatr Soc* 2004 Aug;52:1277-1283.
- (20) Steinberg M, Shao H, Zandi P, et al. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. *Int J Geriatr Psychiatry* 2008 Feb;23:170-177.
- (21) Aneshensel CS, Pearlin LI, Mullan J.T., Zarit SH, Whitlach C.J. *Profiles in caregiving: The unexpected career*. San Diego: Academic Press, 1995.
- (22) Schulz R, Williamson GM. A 2-year longitudinal study of depression among Alzheimer's caregivers. *Psychol Aging* 1991 Dec;6:569-578.
- (23) Baumgarten M, Hanley JA, Infante-Rivard C, Battista RN, Becker R, Gauthier S. Health of family members caring for elderly persons with dementia. A longitudinal study. *Ann Intern Med* 1994 Jan 15;120:126-132.
- (24) Li LW, Seltzer MM, Greenberg JS. Change in depressive symptoms among daughter caregivers: an 18-month longitudinal study. *Psychol Aging* 1999 Jun;14:206-219.
- (25) Ballard CG, Saad K, Coope B, et al. The aetiology of depression in the carers of dementia sufferers. *Journal of Affective Disorders* 1995 Oct 9;35:59-63.
- (26) Brodaty H, Luscombe G. Psychological morbidity in caregivers is associated with depression in patients with dementia. *Alzheimer Dis Assoc Disord* 1998 Jun;12:62-70.

- (27) Harwood DG, Barker WW, Cantillon M, Loewenstein DA, Ownby R, Duara R. Depressive symptomatology in first-degree family caregivers of Alzheimer disease patients: a cross-ethnic comparison. *Alzheimer Dis Assoc Disord* 1998 Dec;12:340-346.
- (28) Heok KE, Li TS. Stress of caregivers of dementia patients in the Singapore Chinese family. *International Journal of Geriatric Psychiatry* 1997 Apr;Vol.12:466-469.
- (29) Neundorfer MM, McClendon MJ, Smyth KA, Stuckey JC, Strauss ME, Patterson MB. A longitudinal study of the relationship between levels of depression among persons with Alzheimer's disease and levels of depression among their family caregivers. *J Gerontol B Psychol Sci Soc Sci* 2001 Sep;56:301-313.
- (30) Allegri RF, Sarasola D, Serrano CM, et al. Neuropsychiatric symptoms as a predictor of caregiver burden in Alzheimer's disease. *Neuropsychiatr Dis Treat* 2006 Mar;2:105-110.
- (31) Elmstahl S, Ingvad B, Annerstedt L. Family caregiving in dementia: prediction of caregiver burden 12 months after relocation to group-living care. *Int Psychogeriatr* 1998 Jun;10:127-146.
- (32) Gallagher-Thompson D, Brooks JO, III, Bliwise D, Leader J, Yesavage JA. The relations among caregiver stress, "sundowning" symptoms, and cognitive decline in Alzheimer's disease. *J Am Geriatr Soc* 1992 Aug;40:807-810.
- (33) Gonzalez-Salvador MT, Arango C, Lyketsos CG, Barba AC. The stress and psychological morbidity of the Alzheimer patient caregiver. *International Journal of Geriatric Psychiatry* 1999 Sep;Vol.14:701-710.
- (34) Grafstrom M, Winblad B. Family burden in the care of the demented and nondemented elderly--a longitudinal study. *Alzheimer Dis Assoc Disord* 1995;9:78-86.
- (35) Lim PPJ, Sahadevan S, Choo GK, Anthony P. Burden of caregiving in mild to moderate dementia: An Asian experience. *International Psychogeriatrics* 1999 Dec;Vol.11:411-420.
- (36) Lim YM, Son GR, Song JA, Beattie E. Factors affecting burden of family caregivers of community-dwelling ambulatory elders with dementia in Korea. *Arch Psychiatr Nurs* 2008 Aug;22:226-234.
- (37) Magai C, Cohen CI. Attachment style and emotion regulation in dementia patients and their relation to caregiver burden. *J Gerontol B Psychol Sci Soc Sci* 1998 May;53:147-154.
- (38) Onishi J, Suzuki Y, Umegaki H, Nakamura A, Endo H, Iguchi A. Influence of behavioral and psychological symptoms of dementia (BPSD) and environment of care on caregivers' burden. *Arch Gerontol Geriatr* 2005 Sep;41:159-168.

- (39) Reis MF, Gold DP, Andres D, Markiewicz D, Gauthier S. Personality traits as determinants of burden and health complaints in caregiving. *Int J Aging Hum Dev* 1994;39:257-271.
- (40) Shaji KS, George RK, Prince MJ, Jacob KS. Behavioral symptoms and caregiver burden in dementia. *Indian J Psychiatry* 2009 Jan;51:45-49.
- (41) Donaldson C, Tarrrier N, Burns A. Determinants of carer stress in Alzheimer's disease. *International Journal of Geriatric Psychiatry* 1998 Apr;Vol.13:248-256.
- (42) LoGiudice D, Waltrowicz W, McKenzie S, Ames D, Flicker L. Prevalence of dementia among patients referred to an aged care assessment team and associated stress in their carers. *Aust J Public Health* 1995 Jun;19:275-279.
- (43) Pearlin LI, Mullan JT, Semple SJ, Skaff MM. Caregiving and the stress process: an overview of concepts and their measures. *Gerontologist* 1990 Oct;30:583-594.
- (44) Hooker K, Bowman SR, Coehlo DP, et al. Behavioral change in persons with dementia: relationships with mental and physical health of caregivers. *J Gerontol B Psychol Sci Soc Sci* 2002 Sep;57:453-460.
- (45) Son J, Erno A, Shea DG, Femia EE, Zarit SH, Stephens MA. The caregiver stress process and health outcomes. *J Aging Health* 2007 Dec;19:871-887.
- (46) Goode KT, Haley WE, Roth DL, Ford GR. Predicting longitudinal changes in caregiver physical and mental health: a stress process model. *Health Psychol* 1998 Mar;17:190-198.
- (47) Mittelman MS, Roth DL, Haley WE, Zarit SH. Effects of a caregiver intervention on negative caregiver appraisals of behavior problems in patients with Alzheimer's disease: results of a randomized trial. *J Gerontol B Psychol Sci Soc Sci* 2004 Jan;59:27-34.
- (48) Schulz R, Hebert RS, Dew MA, et al. Patient suffering and caregiver compassion: new opportunities for research, practice, and policy. *Gerontologist* 2007 Feb;47:4-13.
- (49) Stern Y, Folstein M, Albert M, et al. Multicenter study of predictors of disease course in Alzheimer disease (the "predictors study"). I. Study design, cohort description, and intersite comparisons. *Alzheimer Dis Assoc Disord* 1993;7:3-21.
- (50) McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984 Jul;34:939-944.
- (51) Stern Y, Sano M, Paulson J, Mayeux R. Modified Mini-Mental State Examination: validity and reliability. *Neurology* 1987;37:179.

- (52) Folstein MF, Folstein SE, McHugh PR. Mini mental state: A practical state for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-198.
- (53) McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* 1996 Nov;47:1113-1124.
- (54) Derogatis L. The Brief Symptom Inventory (BSI): Administration, scoring and procedures manual, 3rd ed. Minneapolis, MN: NCS Pearson, 1993.
- (55) Nunnally J, Bernstein I. Psychometric Theory, 3rd ed. New York: McGraw Hill, 1994.
- (56) Devanand DP, Miller L, Richards M, et al. The Columbia University Scale for Psychopathology in Alzheimer's disease. *Arch Neurol* 1992 Apr;49:371-376.
- (57) Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry* 1968 Jul;114:797-811.
- (58) Stern Y, Albert SM, Sano M, et al. Assessing patient dependence in Alzheimer's disease. *J Gerontol* 1994 Sep;49:M216-M222.
- (59) Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-383.
- (60) Marcus R, Marder K, Bell K, Dooneief G, Mayeux R, Stern Y. Interrater Reliability of Extrapyrmidal Signs in a Group Assessed for Dementia. *Arch Neurol* 1991;48:1147-1149.
- (61) Stern Y, Tang MX, Albert MS, et al. Predicting time to nursing home care and death in individuals with Alzheimer disease. *JAMA* 1997 Mar 12;277:806-812.
- (62) Scarmeas N, Hadjigeorgiou GM, Papadimitriou A, et al. Motor signs during the course of Alzheimer disease. *Neurology* 2004 Sep 28;63:975-982.
- (63) Higginson IJ, Gao W, Jackson D, Murray J, Harding R. Short-form Zarit Caregiver Burden Interviews were valid in advanced conditions. *J Clin Epidemiol* 2010 May;63:535-542.
- (64) Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986 Dec;51:1173-1182.
- (65) Rindskopf D. Linear equality restrictions in regression and loglinear models. *Psychological Bulletin* 1984;96:597-603.

- (66) Alexopoulos GS, Abrams RC. Depression in Alzheimer's disease. *Psychiatr Clin North Am* 1991 Jun;14:327-340.
- (67) Lyketsos CG, Steele C, Baker L, et al. Major and minor depression in Alzheimer's disease: prevalence and impact. *J Neuropsychiatry Clin Neurosci* 1997;9:556-561.
- (68) Gellis Z, McClive-Reed K, Brown E. Treatments for depression in older adults with depression. *Ann Long Term Care* 2009;17:9-10.
- (69) Woods B, Thorgrimsen L, Spector A, Royan L, Orrell M. Improved quality of life and cognitive stimulation therapy in dementia. *Aging Ment Health* 2006 May;10:219-226.
- (70) Hoe J, Hancock G, Livingston G, Orrell M. Quality of life of people with dementia in residential care homes. *Br J Psychiatry* 2006 May;188:460-464.
- (71) Monin JK, Schulz R. Interpersonal effects of suffering in older adult caregiving relationships. *Psychol Aging* 2009 Sep;24:681-695.
- (72) Schulz R, McGinnis KA, Zhang S, et al. Dementia patient suffering and caregiver depression. *Alzheimer Dis Assoc Disord* 2008 Apr;22:170-176.
- (73) Chiu MJ, Chen TF, Yip PK, Hua MS, Tang LY. Behavioral and psychologic symptoms in different types of dementia. *J Formos Med Assoc* 2006 Jul;105:556-562.
- (74) Stavitsky K, Brickman AM, Scarmeas N, et al. The progression of cognition, psychiatric symptoms, and functional abilities in dementia with Lewy bodies and Alzheimer disease. *Arch Neurol* 2006 Oct;63:1450-1456.
- (75) Weiner B. An attributional theory of motivation and emotion. New York: Springer-Verlag, 1986.
- (76) Watson LC, Lewis CL, Moore CG, Jeste DV. Perceptions of depression among dementia caregivers: findings from the CATIE-AD trial. *Int J Geriatr Psychiatry* 2010 Sep 15.
- (77) Teri L. Behavior and caregiver burden: behavioral problems in patients with Alzheimer disease and its association with caregiver distress. *Alzheimer Dis Assoc Disord* 1997;11 Suppl 4:S35-S38.
- (78) Teri L, McCurry SM, Logsdon R, Gibbons LE. Training community consultants to help family members improve dementia care: A randomized controlled trial. *The Gerontologist* 2005 Dec;Vol.45:802-811.
- (79) Martire LM, Lustig AP, Schulz R, Miller GE, Helgeson VS. Is it beneficial to involve a family member? A meta-analysis of psychosocial interventions for chronic illness. *Health Psychol* 2004 Nov;23:599-611.

Chapter 3:

The timing of behavioral and psychological symptoms in the dementia patient and the course of caregiver depressive symptoms

Abstract

The behavioral and psychological symptoms associated with dementia (BPSD) are burdensome to caregivers, negatively affecting mental health and impacting decisions to institutionalize patients. Because the dementia patient-caregiver relationship extends over long periods of time, it may be useful to examine how BPSD impact caregiver depressive symptoms at varied stages of illness and how symptom changes impact change in caregiver outcomes. The goals of this paper are to: assess the role of BPSD that occur during early stage dementia on the development of subsequent caregiver depressive symptoms; characterize the course of depressive symptoms among caregivers over time; and examine the relationship between change in patient depressive symptoms and change in caregiver depressive symptoms. Patient-caregiver dyads were followed from the early stages of dementia every six months for up to 12 years or until death (n=160). A generalized estimating equation (GEE) extension of the logistic regression model was used to determine the association between four individual BPSD symptoms at early stages of dementia and subsequent caregiver depression. Growth mixture modeling (GMM) was used to identify trajectories of caregiver depression over time. Logistic regression models were used to determine the relationship between change in patient depressive symptoms and change in caregiver depressive symptoms. The presence of BPSD at early dementia did not impact subsequent caregiver depressive symptoms. Overall, most caregivers had stable trajectories of symptoms, with a smaller subset showing more evidence for wear-and-tear over time. There was no evidence for an association between change in patient depressive symptoms and change in caregiver depressive symptoms. Future work should utilize a longitudinal perspective on caregiving to identify whether similar patterns hold for other individual BPSD and caregiver

outcomes. Those caregivers who follow a wear-and-tear trajectory over time may require targeted interventions to improve their outcomes.

Introduction

As life expectancy increases in the United States and internationally, the aging population and therefore the number of people living with chronic diseases such as dementia continues to grow.(1) According to recent estimates, as many as 5.3 million Americans have Alzheimer's Disease (AD).(2) Consequently, the number of family members providing informal (i.e., non-professional or family) caregiving to individuals with dementia has also increased to almost 11 million.(2-4) While family caregivers provide a critical service to family members in lieu of more formal sources of long-term care support, they often suffer from chronic stress which results in negative consequences for the caregiver's mental and physical health.(5-8) Although cognitive decline is considered the clinical hallmark of dementia, an extensive body of literature suggests that the non-cognitive, or the behavioral and psychological symptoms associated with dementia (BPSD), may be more burdensome to caregivers and may eventually lead to decisions to institutionalize patients.(5;9-15) BPSD, which consist of a wide variety of patient behaviors including depression, physical aggression and paranoid delusions, are highly prevalent in patients with dementia over the course of their illness.(16-20)

The patient-caregiver relationship is extending as patients are living longer with chronic illnesses such as dementia. The average caregiver serves in their caregiving capacity for 4.3 years.(3) Forty percent of caregivers report providing assistance for five or more years, and nearly one-fifth report doing so for more than ten years.(21) Caregivers of people with AD and other dementias provide more hours of help, on average, than caregivers of other older people, and serve in their caregiving role for longer periods of time.(3;4) Yet the majority of studies on dementia caregiving are cross-sectional.(5;10) Relatively few analyses adopt longitudinal designs to determine potential predictors of caregiver psychosocial adaptation over time.

Moreover, most of the existing studies on caregiving and BPSD consider BPSD only at a single point during the course of disease progression, most typically at the baseline visit.(9) Such a limited focus on symptom occurrence is problematic given that these features are known to vary over the course of illness because of the progressive nature of dementia.(19;22) Furthermore, given the wide variation in symptoms grouped together within BPSD, it may be more useful to consider the long-term impact of individual symptom clusters of BPSD. Establishing how timing of behavior impacts caregiver response is paramount to understanding the etiology of caregiver depression and developing effective interventions appropriate to the changing course of disease. This includes considering (1) the potential for sensitive time periods in the patient-caregiver relationships that may have lasting impact on caregiver outcomes and (2) the dynamic relationship between patient behavior and caregiver depression that we can only see over time.

Significance of timing of BPSD: the role of early behaviors

Within life course approaches to epidemiology, the concept of a sensitive time period refers to a time period during which an exposure has a greater effect than outside the period.(23) Within the patient-caregiver relationship, the beginning of the relationship may be a sensitive time period relative to negative caregiving outcomes. Unexpected entry into roles is known to be disruptive for individuals(24); this finding may be especially salient for those individuals who enter the official “unexpected career” of caregiving. Research suggests that among caregivers, those who have a more unexpected transition into their role have increased risk of depression and are more likely to institutionalize patients.(25) Additionally, studies find that earlier age of onset of disease is associated with earlier nursing home placement for AD patients.(26;27) Finally, Gaugler et al.(28) found that low resilience early in the caregiving career was associated with relinquishing the caregiver role at three years follow-up suggesting that the caregiver’s

experience early in the patient's illness may be predictive of later outcomes. Together, these findings point to the critical importance of timing in understanding caregiving outcomes, and, in particular, suggest that challenges that occur early in the caregiving career when signs of illness first appear may have lasting impact for the caregivers over the course of the patient's illness. The unpredictable nature of BPSD, for example, may severely tax resources of caregivers new to their role such that features that occur early in the disease process may impact caregiver depression independent of subsequent changes in disease course.

The one study that examined the impact of BPSD early in the caregiver-patient relationship(29) reported that severe behavior symptoms early in caregiving were independent predictors of increased burden and depression over three years regardless of later BPSD development. This study, however, like most caregiving research studies, did not follow patients from disease onset, instead relying on caregiver reports of care duration. We therefore do not know how symptoms that occur early in the disease course impact subsequent caregiver outcomes. Further research is warranted which uses clinician estimates of illness duration to assess how the timing of BPSD manifestations overall, and individual BPSD in particular, impact depression outcomes for the caregiver, especially over longer periods of time. By studying the impact of timing of behaviors, we may be able to focus on specific stages of the patient-caregiver relationship in which intervention for caregivers would be most beneficial. Additionally, given concerns about lack of safe long-term pharmacotherapy to treat BPSD,(30) knowledge of whether individual behaviors that occur early in the dementia process independently impact subsequent caregiver outcomes may direct current treatment protocols.

The caregiving role over time

The stress process model has been used to conceptualize caregiving as an exposure to multiple long-term stressors.(31) Given this, stress appraisals (i.e., how difficult the caregiver perceives the stressor to be) may be expected to become more negative over time with increasing negative repercussions for mental health. This model is known as the “wear and tear” model of caregiving.(32) Over time, caring for the patient and managing the increased functional limitations and BPSD becomes more difficult for the caregiver resulting in increased depression. An alternative to this hypothesis is “adaptation”(32) which proposes that over time caregivers adapt to stressful situations and become less negative in their stress appraisals. In other words, the caregiver adapts to the cognitive changes in the patient and may consequently change expectations for their relationship with the patient which mitigates negative effects of the stressor. Caregivers can acclimate to their circumstances, experiencing little change or even improvement over time. While the caregiver may initially find it difficult to accept that their spouse is prone to verbal outbursts and is easily agitated, over time they may become more tolerant of these behaviors and appreciate the limited positive interactions they have with the patient. Finally, caregivers may also maintain a constant level of adjustment despite worsening of symptoms, suggesting that mood is constant or stable despite changing stressors over time.

The majority of longitudinal studies of depression in caregivers of patients with dementia suggest that overall caregivers have stable levels of depression over time(7;33-35) and provide little evidence for caregivers experiencing variability in trajectories, e.g., wear-and-tear.

Subgroups of caregivers may experience different courses of symptoms over time such that some may adapt to their roles whereas others may follow a wear-and-tear trajectory. Studies of caregiver bereavement, for example, have identified multiple and distinct trajectories of caregiver depressive symptoms following a patient’s death.(36;37) Studies of caregivers caring

for dementia patients have not distinguished between groups of caregivers to determine if there are varied symptom trajectories.

The impact of BPSD, overall and individually, on the adaptation process is not understood. Determining how the relationship between BPSD and caregiver depression changes over time is important given that it is clear that individual BPSD have varied trajectories over the course of patient illness.(38;39) The few studies that have examined this relationship over time yield mixed findings. Over four years Mittelman et al.(40) found that stress related to BPSD increased over time; similarly, other studies have found increases in depression(41-44) or burden(45;46) as BPSD increase over time. On the other hand, Goode et al.(34) found caregiver outcomes were stable over one year and Li et al.(47) found that among daughter caregivers, BPSD were associated with decreased mastery but had no effect on depression as measured over 18 months. Over shorter time periods (i.e., three months), researchers have found evidence for stability in stress relative to BPSD.(48) While the evidence suggests more support for wear-and-tear for caregivers relative to the occurrence of BPSD, findings remain inconclusive and warrant further investigation. This is largely due to studies including patients at various stages of illness, thus grouping together new caregivers and those who have been caring for patients for many years. Additionally, studies do not routinely control for the impact of third variables, and many studies only examine change across two time points (34;41-43;46;47) which may fail to capture a more complex non-linear relationship over time. Furthermore, only two studies have examined caregiver outcomes over time relative to any individual behavioral symptom or symptom clusters.(44;49) By grouping together all symptoms, researchers may be obscuring those relationships in which individual symptoms are significantly driving negative caregiver outcomes.

As our previous cross-sectional research found that patient depressive symptoms had the strongest effect on caregiver depression at any time point,(50) we were particularly interested in whether change in patient depressive symptoms impact the course of caregiver depressive outcomes over time.

Study Aims

The overall aims of this study are to examine the relationship between BPSD symptom clusters and caregiver depressive symptoms over time. Specifically, we will assess the role of BPSD symptoms that occur early in dementia patients on the development of subsequent caregiver depressive symptoms. We hypothesize that BPSD symptoms that occur early in the course of dementia will affect the development of subsequent caregiver depressive symptoms. Second, we will characterize the course of depressive symptoms among caregivers over time and determine if there are distinct symptom trajectories. Finally, we will examine the relationship between change in patient depressive symptoms and change in caregiver depressive symptoms. We hypothesize that caregiver depressive symptoms will increase relative to increases in patient depressive symptoms over time.

Methods

Sample

The Predictors 2 cohort consists of patients with probable AD and Dementia with Lewy Bodies (DLB) who were followed prospectively from early stages of patient illness. Patients were recruited from memory disorder centers or private physician offices in three sites between 1997 and 2008: Columbia University College of Physicians and Surgeons; Johns Hopkins University

School of Medicine; and Massachusetts General Hospital. The inclusion and exclusion criteria and evaluation procedures of the Predictors study have been fully described elsewhere.(51) Briefly, all patients were diagnosed in a consensus conference with at least two faculty physicians specializing in dementia and one faculty neuropsychologist. All AD patients met NINCDS-ADRDA criteria for probable AD(52) and intellectual impairment was documented with neuropsychological testing. At entry into study, each AD participant was required to have relatively mild dementia operationalized as a modified Mini Mental State Examination (MMSE) (53) score ≥ 30 , equivalent to a score of ≥ 16 on the Folstein MMSE.(54) Patients with DLB were diagnosed according to the 1996 consensus guidelines for the disease.(55) Participants were also required to have at least one family member/informant available. Exclusion criteria were parkinsonism, stroke, alcoholism, schizophrenia, schizoaffective disorder, and electroconvulsive treatments.

During an initial visit, the following data were collected about the patient via clinical assessment: patient demographic data, medical history, neurological evaluation, handedness, presenting features of cognitive impairment, functional status, family history of dementia, onset dating and features, and BPSD. Follow-up data were collected at 6-month intervals via inpatient visit thereafter until dropout or death including: neurological evaluation, functional and cognitive status, medical and psychiatric history, and quality of life. If patients were unable to travel to the outpatient clinic for evaluation, they were visited at their homes, nursing homes, or health care facilities. There is 94% follow up of patients. Patients who did not respond at a particular visit could respond at a subsequent visit. Autopsy data were also collected when possible to confirm diagnoses.

The Predictors Caregiver study was initiated in 2004. (See Appendix 3.A for diagram of study design and follow-up.) Detailed data on the demographics, mental health status of the informal caregivers of the Predictors 2 patient cohort, as well as the amount and level of care provided were collected for 160 patient-caregiver dyads at study baseline. Follow-up data on caregiver mental health status, level of care, and living situation were collected at six month intervals up to six years simultaneous to the collection of data on patient cognitive, functional, and BPSD symptoms on the entire Predictors 2 cohort. A total of 169 patients were active in the Predictors 2 cohort at the time of, or subsequent to, the launching of the Caregiver study. Of these patients, six did not have an eligible informal caregiver to complete the study (3.6%). Of the 163 eligible patient-caregiver dyads, 98.2% have caregiver data available for at least one assessment; three caregivers refused to answer questions on their experiences as a caregiver. When necessary, patient and caregiver data were collected post-institutionalization. While the study is ongoing, this analysis includes data collected through August 2010. On average there were 4.2 assessments per caregiver, allowing for 80% power to detect odds ratios of at least 2.0 in caregiver depressive symptoms for each symptom cluster(50) and allowing for sufficient data points for longitudinal analysis involving latent curve modeling.(56)

Measures

Outcome measures

Caregiver depressive symptoms were measured at six month intervals by the six-item depression subsection of the brief symptom inventory (BSI).(57) Caregivers were asked how much during the past week they were bothered by the following: feeling lonely, feeling blue, feeling no interest in things, feeling hopeless about the future, feelings of worthlessness, and thoughts of

ending your life using a five-point Likert scale response for each item ranging from “not at all” to “extremely”. A higher score indicates higher depressive symptoms. The mean score across six symptoms was calculated (mean=1.44, standard deviation (SD) =0.56) as a continuous variable. The standardized Cronbach’s coefficient alpha was $>.80$ indicating acceptable reliability.(58) Mean BSI score was also dichotomized as no depressive symptoms (<2) and depressive symptoms (≥ 2) for use in logistic regression analysis. Caregivers categorized as having depressive symptoms were (1) one SD above the mean depressive symptom score and (2) indicated that on average each of the six symptoms bothered or impacted them from a minimal to extreme level.

Change in caregiver depression was categorized as a three-level ordinal variable depending on whether caregiver depressive symptoms decreased, stayed the same or increased over time. Using the first and last recorded caregiver depression assessment, “increased” was defined as moving up a quartile; “decreased” defined as moving to a lower quartile; and “same” defined as staying in the same quartile. Caregiver depressive symptoms were treated as a continuous variable (range 1-3.5) and quartile cut-offs were as follows: quartile I=1; quartile II=1.01-1.17; quartile III=1.18-1.67; quartile IV=1.68-3.5). We also calculated a change score for caregiver depressive symptoms using first and last recorded caregiver depression assessment per caregiver (positive score indicating an increase in symptoms, 0 indicating no change, and a negative score indicating a decrease in symptoms)

Exposure measures

Early patient dementia behaviors

At entry to Predictors Study, when patients were in early stages of dementia, The Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD)(59) was used to measure patient BPSD. The CUSPAD is a semi-structured rating scale that a clinician or research assistant administers to the informant regarding the presence of 26 patient symptoms during the last month before each interview. Interrater reliabilities for individual symptoms range from kappa coefficients of .61-.73.(59)

Four non-overlapping symptom clusters based on a review of the literature and the hypothesized differential impact of symptom clusters on caregivers were created. (See chapter 1 for justification of individual symptom clusters.)

1. Accusatory and aggressive symptoms were measured based on the following six CUSPAD items designed to measure paranoid and abandonment delusions as well as aggression: beliefs that people are stealing things, beliefs that they have an unfaithful wife/husband, other unfounded suspicions, accusing caregiver of plotting to leave him/her, engaging in threatening behavior, and engaging in physical violence. Given that these behaviors may be directed at the caregivers and are unlikely to be easily ignored, they may be particularly disturbing to the caregivers. We constructed a dichotomous variable to characterize the presence or absence of one or more accusatory and aggressive symptoms.

2. Non-threatening psychotic symptoms consisted of the following 13 items which constitute the remainder of the psychotic symptoms (hallucinations, illusions, misidentification delusions and somatic delusions) measured in the CUSPAD: belief that the patient has cancer or other physical illness, belief that people are in the house when nobody is there, belief that someone else is in the mirror, belief that the spouse/caregiver is an imposter, belief that the patient's house is not his/her

home, belief that the characters on television are real, report that one thing is something else, hearing voices when no one is there, seeing visions; reporting unusual smells, and other reports of false beliefs or strange ideas or hallucinations. These items are categorized as non-threatening because while they are by definition psychotic, and likely disturbing to the caregiver because they are non-normative, they are not directly threatening the caregiver. We constructed a dichotomous variable to indicate the presence or absence of any non-threatening psychotic symptoms.

3. *Depressive symptoms*: Patient depressive symptoms were defined as having (1) depressed mood and (2) either difficulty sleeping or change in appetite. We constructed a dichotomous variable indicating the presence or absence of patient depressive symptoms.

4. *Difficult to manage behaviors*: The presence of difficult to manage behaviors was dichotomized to indicate the presence or absence of one or more of the following four behaviors: wandering away from home or from the caregiver, showing agitation or restlessness, making verbal outbursts, and sundowning (increased disorientation, restlessness, agitation in the late afternoon or evening).

Any early dementia behavior

Finally, we created a dichotomous variable (present/absent) to indicate the presence of any of the above four individual symptom behaviors presenting at cohort inception. We also created an ordinal variable (range=0-4) indicating the number of symptom clusters present at baseline.

Change in patient depressive symptoms:

Patient depressive symptoms were measured as an ordinal variable at all intervals throughout the Caregiver study. A score for patient depression (range=0-4) was created using CUSPAD items described above based on overall depressed mood, presence of other depressed symptoms (difficulty sleeping, change in appetite) and frequency of depressed mood (more than occasionally). We categorized change in patient depressive symptoms at the start of the Caregiver study from first to last patient depression assessment as a three-level outcome (increase, decrease, same). While quartiles for patient depression (assessed as a continuous variable ranging from 0-4) were computed, because of a high proportion of zero values, the variable was dichotomized as 0 and ≥ 1 to determine whether score increased, decreased or stayed the same over time. We also calculated a change score for patient depressive symptoms using first and last recorded patient depression assessment (positive score indicating an increase in symptoms, 0 indicating no change, and a negative score indicating a decrease in symptoms).

Patient and caregiver characteristics

The following patient and caregiver characteristics were examined as potential confounding variables and as sources of variation among groups of patient-caregiver dyads:

Patient cognitive status was assessed at study baseline and each subsequent visit using the MMSE(54) in which higher MMSE score indicates better cognitive status. Patient functional status was assessed at each visit using parts I and II of the Blessed Dementia Rating Scale (BDRS).(60) Part I assesses instrumental activities of daily living (IADL) (i.e., shopping, housekeeping) and has a maximum score of 8, indicating the lowest level of function. Part II measures basic activities of daily living (ADL) (i.e., eating, dressing, and toileting) and has a maximum score of nine. Patients' medical histories were used to construct a modified version of

the Charlson index of comorbidity.(61) Comorbidities included myocardial infarction, congestive heart failure, peripheral vascular disease, hypertension, chronic obstructive pulmonary disease, arthritis, gastrointestinal diseases, mild liver disease, diabetes, chronic renal disease, and systemic malignancy. A modified Unified Parkinson's Disease Rating Scale(26;62) was administered at each visit to measure the presence or absence of extrapyramidal signs (EPS)(e.g., tremors, rigidity). Following previous work,(63) a dichotomous indicator was constructed for the use of EPS if any of the following 11 items were rated 2 or higher (0 being normal and 4 indicating maximum impairment): speech, facial expression, tremor at rest, neck rigidity, right arm rigidity, left arm rigidity, right leg rigidity, left leg rigidity, posture, gait, and bradykinesia). Patient age, ethnicity, sex, and highest level of education were recorded at the inception of the Predictors cohort; marital status was recorded at each visit. Duration of illness in years was estimated by a neurologist based on baseline interviews with the patient and caregiver.

Caregiver age, gender, and relationship to patient (spouse vs. non-spouse) were recorded at Caregiver study baseline. Whether the caregiver lives with the patient and frequency of contact with patient were recorded at each visit. Whether caregiver assists with basic and instrumental activities of daily living, the amount of hours the patient spends per day with the caregiver, whether a home health aide/home attendant assisted with care and caregiver's employment status were reported annually. We imputed missing data for six month (or semi-annual) intervals by using subsequent visit annual caregiver data scores when available. This conservative approach assumes caregivers are providing more services as patient functional status declines over time.

Statistical analysis

Timing of behaviors

To determine the relationship between early patient dementia behaviors and subsequent caregiver depressive symptoms, we tested the impact of four individual patient symptom clusters when patients had early stages of dementia on subsequent caregiver depressive symptoms. Using all time point assessments available after the baseline assessment (n=637) for 160 patient caregiver dyads, we tested the relationship between individual early dementia behaviors and caregiver depressive symptoms (1)unadjusted, (2)controlling for behavior symptoms concurrent to caregiver depression, and (3)controlling for potential confounding variables and all concurrent patient behavior symptoms. To account for repeated measures per dyad, we used a logistic model with a generalized estimating equation (GEE) extension. On average early dementia patient behavior symptoms were measured 4.5 years prior to follow-up caregiver depression assessments (range= six months to 12 years). To determine which variables would be included in the final model, bivariate associations between (1) caregiver depressive symptoms and potential confounders and (2) individual early dementia BPSD and potential confounders were assessed. Only those variables that showed a statistically significant effect on the outcome at the 0.10 level, were associated with at least one symptom cluster, and were not highly correlated with other variables (correlation >.5) in the bivariate analysis were included in the final adjusted model. We also tested the impact of the presence of at least one behavior symptoms at early stage of patient dementia illness on subsequent caregiver depressive symptoms in a multivariate logistic GEE model. Any early dementia patient behaviors symptoms were tested as both a dichotomous variable (present/absent) and ordinal variable (range from 0-4).

Characterizing symptom trajectories

Course of caregiver depressive symptoms: We used growth mixture modeling (GMM) to analyze change in caregiver depression at six month assessments over six years of follow-up using caregiver depressive symptoms as a dichotomous variable. GMM tests whether more than one distinct class can be used to describe the data. Each class possesses unique latent factors of growth that distinguishes subjects from those in a different subpopulation. GMM makes use of all data despite attrition using the Full Information Maximum Likelihood method (FIML). We used the customized SAS procedure TRAJ to identify and describe distinct patterns of trajectories in caregiving depression.(64)

We first estimated a model with an intercept only and then added a linear and cubic growth factor to determine the form of the growth model. We then proceeded to identify the number of trajectory classes. The number of trajectory classes is determined by sequentially increasing the number of classes, and examining the results and fit statistics. The optimal number of groups to form relatively homogenous clusters with similar trajectories are determined using Bayesian Information Criteria, with smaller values indicating better fit.(64;65) Because group membership is probabilistic (i.e., not observed), misclassification may occur and probabilities of group assignment must be evaluated. Posterior probabilities of belonging to each of the hypothetical groups defined by the trajectories were calculated from model parameter estimates, and the highest value was used to assign each caregiver to one group.(66)

After determining the number of trajectory classes, we examined the bivariate associations between the emerging caregiver depression classes and early patient dementia behaviors, patient demographic and clinical features, and caregivers' demographic characteristics and level of care

using chi-square tests for categorical variables, t-tests for normal continuous variables, and Kruskal Wallis test for non-normal continuous variables.

Course of patient depressive symptoms: GMM was also used to categorize patient depression trajectories occurring parallel to the caregiver trajectories (see previous section for description of technique).

Change in patient depression and change in caregiver depression

Two techniques were used to examine the relationship between simultaneous change in patient depression and caregiver depression symptoms: (1) We used a polytomous logistic regression with a cumulative logit link function analysis with three-level outcome to test whether change in patient depressive symptoms (increase, decrease, same) predicts change in caregiver depression; the latter was also defined as a 3-level ordinal variable (increase, decrease, same). Patient depression values corresponded to first and last recorded caregiver assessments. (2) Next, we used a logistic regression analysis to determine whether change in patient depression score was predictive of caregiver depression trajectory status. Change scores from first to last patient depression assessment were calculated and included as independent risk factors.

All analyses were conducted using SAS version 9.2.

Results

Timing of behaviors

Contrary to our hypothesis, early dementia patient behavior symptoms did not impact subsequent caregiver behaviors. As shown in Table 3.1, none of the four individual early patient dementia

symptom clusters examined had significant impact on caregiver depressive symptoms unadjusted, or when controlling for concurrent patient individual behaviors. Furthermore, the presence of any BPSD in the earliest stages of illness did not independently impact caregiver depressive symptoms when controlling for potential confounding variables (OR= 1.14; 95% CI=.67-1.94). Similarly, no association was found when BPSD in earliest stages of illness was examined as an ordinal variable (see Appendix 3.B).

Course of caregiver depressive symptoms

Caregiver depression data with at least two time points for analysis of longitudinal data were available for n=133 patient-caregiver dyads. The mean number of assessments available per caregiver was 4.84 (median=4). Twenty-two percent of caregivers had two assessments (n=29); 17% had three assessments (n=22); 14% had four assessments (n=18); 12% had five assessments (n=16); 8% had six assessments (n=10); 14% had seven assessments (n=19); and 14% had between eight and 12 assessments completed (n=19).

Overall we found that caregiver depression scores more often stayed the same or increased over time, with a much smaller percentage showing a decrease. Using change in quartile between first and last caregiver assessment, caregiver depression over time was categorized as same (n=56; 42.11%), increased (n=55; 41.35%), and decreased (n=22; 16.54%). Similarly, using a measure of absolute change score between first and last recorded caregiver assessment, 79% of caregivers had the same or an increase in depressive symptoms over time while only 21% had a decrease in depressive symptoms. The mean caregiver assessment score at baseline was 1.33 (SD=.53) and at last assessment was 1.51 (SD=.61). The average change score from first to last caregiver assessment was .18 (SD=.20) ranging from -2.00 to 1.83.

Trajectories

We were unable to visually discern a clear pattern of adaptation or wear-and-tear among caregivers after plotting the course of depressive symptoms for each caregiver using all available data points (Figure 3.1). Using GMM, we identified two trajectories of caregiver depressive symptoms (Figure 3.2) which are depicted graphically with 95% confidence intervals. The most common trajectory represented 69% of all caregivers (n=92) and was characterized by a consistently low probability of having depressive symptoms stable over every time point (hereafter called “stable caregivers”). The remainder of the sample (n=41; 31%) consisted of caregivers with a higher baseline risk of depression with a slight but steady increase over time in risk of depressive symptoms (hereafter called “wear-and-tear caregivers”). The three trajectory model examined included a small additional group (<5% of caregivers) that had a steeper increase in symptoms before stabilizing over time in addition to the aforementioned groups of stable and wear-and-tear caregivers. However, standard fit statistics determined that the two trajectory class model best described the data (Table 3.2).

The average posterior probability of membership was 91% (stable caregivers) and 95% (wear-and-tear caregivers) suggesting a good level of correct group assignment. Minimum probabilities are all well above .50 suggesting that caregivers assigned to a group are more likely to belong to that group than not.

Characteristics of groups defined by depressive symptom trajectories

As shown in Table 3.3, caregiver trajectory did not differ based on the presence of individual or cumulative patient BPSD at early dementia diagnosis. In fact, patient clinical characteristics such as cognitive status, functional status, presence of other medical comorbidities or EPS, and

amount of time since dementia diagnosis did not differ for stable and wear-and-tear caregivers. Differences between the groups were instead found to be due to the relationship between the patients and caregivers and the amount of time they spent together. Spouses of male patients and those who spent at least 12 hours a day with the patient at baseline were significantly more likely ($p < .05$) to be wear-and-tear caregivers. There was also a trend for caregivers who were less likely to work, older, and live with the patient to be more likely to experience a wear-and-tear trajectory.

Change in patient depression and change in caregiver depression

Course of patient depressive symptoms: When examining change scores for patient depression ($n=136$), we find little evidence for change over time. Overall patient depression had a mean change score from last to first assessment of $-.09$ ($SD=1.77$). When categorizing depressive symptoms as decreased, same, and worse based on quartile change, we found that the largest group of patients remained the same (53%) and the smallest group appeared to have decreased symptoms over time (19%). Using GMM we found a two-group solution best fit the data ($BIC=-851.51$). The majority of patients (53%) had a higher level of depression which had a slight linear decrease over time ($B= -.06$). The remainder of patients had a very low level of depression at baseline with a small linear increase over time ($B=.12$) (see Figure 3.3). The average posterior probability of membership was high suggesting a good level of correct group assignment.

As shown in Table 3.4, using just first and last recorded caregiver depression assessment, we observed many patterns between change in patient depressive and caregiver depressive symptoms, the most common being no change in patient depression and an increase in caregiver

depressive symptoms (24%) and no change in patient depression and no change in caregiver depression (23%). The least common patterns that emerged were simultaneous decreases in patient and caregiver depression (5%) and increase in patient depression and decrease in caregiver depression (4%).

Using polytomous logistic regression we did not find an association between change in patient depressive symptoms and change in caregiver depressive symptoms in unadjusted models (OR for increase vs. decrease in patient symptoms=0.82; 95% CI= 0.39-1.72). Similarly, change score in patient depression did not impact likelihood of being a wear-and-tear vs. stable depression caregiver (OR=0.96; 95% CI=0.78-1.19).

Discussion

The current study is one of few studies of dementia caregivers to examine the impact of BPSD relative to sensitive time periods in the course of dementia as well as change in caregiver depressive symptoms. We examined the impact of individual and summary measures of BPSD that occurred in mild dementia on subsequent caregiver depression for 160 patient-caregiver dyads for up to 12 years of follow up. The study also characterized the course of caregiver depressive symptoms over time and assessed whether change in one individual BPSD (i.e., patient depressive symptoms) impacted change in caregiver depression.

While we hypothesized that behavior symptoms that occur early in the dementia-caregiver relationship would independently impact subsequent caregiver depression, our findings did not support this hypothesis. While the Predictors 2 cohort is not a dementia inception cohort, patients are enrolled, and by design, assessed at the earliest stages of illness when they have mild dementia. This unique study feature has thus allowed for the first comprehensive assessment of

how individual behaviors that occur early in the patient's illness course may subsequently impact caregiver depression. One previous study demonstrated a relationship between the presence of behavior problems that occurred early in the caregiving career and institutionalization as well as change in caregiver burden and depression.(29) However, this study looked at symptoms reported early in the patient-caregiver relationship, not necessarily those symptoms present in clinically-assessed mild dementia. Furthermore, beyond two years the impact on caregiver depression was more tenuous, suggesting greater need to study the impact of early behavior symptoms over increasing time periods.

Our lack of positive findings does not preclude the possibility that there are other sensitive time periods in the dementia caregiving career in which the occurrence of patient BPSD has lasting and negative impact. We examined the occurrence of BPSD when patients were first diagnosed with AD or DLB and still had high cognitive function (mean baseline MMSE=22.7). It is possible that we need to examine the occurrence of BPSD over the entire first year of diagnosis or at another critical juncture in the patient-caregiver relationship, perhaps at certain thresholds of patient cognitive or functional decline.

Similar to other studies, we found that caregiver level of depression was reasonably stable over time; however, we also found a distinct subset of caregivers who followed a wear-and-tear trajectory of decline. While most work on caregivers over long periods of time estimates one overall trajectory for caregiver symptoms, these findings suggest it may be more useful to identify disparate trajectories among caregivers. Because loss-to-follow-up would bias the study sample to those caregivers who are better able to adjust to their roles, the finding that there is a group of caregivers who have worsening symptoms over time, suggests that this is an important area to continue studying. Because our findings suggest that caregivers do not follow a unique

path over long periods of time, we may want to focus intervention efforts on the wear-and-tear caregivers. In this study, early disease behaviors and other clinical characteristics do not appear to determine the course of caregiver depression. Instead, caregivers who are the wives of patients, who are less likely to work and are spending more time with the patients early in the course of illness, may be at greatest risk for decline. This finding is consistent with past research which finds that women experience greater psychological morbidity from caregiving than men(10;67;68) and that spouses may have a more negative response to dementia behaviors and caregiving responsibilities than adult children.(10) Future work should continue to discern distinct trajectories using extensive periods of follow-up to identify risk factors for long-term decline.

Contrary to our study hypothesis and one previous study examining this relationship(49), we did not find support for an association between change in patient depression and change in caregiver depression. This negative finding was consistent across multiple methodologies employed to test this relationship. In large part, this finding was not surprising given that we found little variability overall in both caregiver depression and patient depression. We also attempted to use latent growth curve modeling(69) to characterize the overall change in caregiver and patient depressive symptoms over time using all available time points. Unfortunately, because of sparse and unaligned data, the growth curve model of caregiver depressive symptoms yielded poor fit (CFI=0; TLI = -0.524) resulting in an inability to estimate reasonable growth curve parameters. Consequently, we were unable to build a model to estimate the impact of change in patient depressive symptoms on caregiver depressive symptoms. Future work in this field may consider using novel non-parametric techniques(70;71) to estimate such growth models utilizing all data points. However, given our lack of findings of even a trend in the direction of an association

using cruder methodology, it is unlikely that more sophisticated modeling techniques will show a positive relationship.

Our study focused on the relationship between change in patient depressive symptoms relative to change in caregiver depression due to previous work that found that patient depressive behavior had the most consistently positive impact on caregiver depressive outcomes;(50) however, future research should examine how change in other individual BPSD behaviors (e.g., aggressive behaviors) may impact change in caregiver depressive symptoms. Further, while we looked at caregiver depressive symptoms as an outcome, because of the well-known consequences that depression has on individuals, it is possible that this relationship may instead more consistently hold for other caregiver outcomes, such as caregiver burden or stress, which should also be further explored. Finally, this work focused on patient-caregiver trajectories, or the course of patient and caregiver symptoms over time. Future work should also examine the role of critical transitions (e.g., nursing home placement, symptom development) that may have long-term consequences for caregiver outcomes.

Strengths and limitations

Because the Predictors Caregiving study was initiated after the inception of the Predictors 2 cohort, we did not have caregiver data concurrent to all measures of patient symptom behaviors resulting in a truncated view of the assessment of change in caregiver symptoms relative to patient symptoms. A more comprehensive view of change in caregiving symptoms relative to change in patient behaviors would begin at disease onset. While this study benefits from being a study of patients at mild dementia, it is not in fact a true dementia inception cohort, i.e., a cohort of patients initially free of dementia. Examination of our findings in a true dementia inception

cohort (e.g., Washington Heights-Inwood Columbia Aging Project(72)) is necessary to truly understand the impact of early diseases features on subsequent caregiver depression behaviors and to examine the impact of early behaviors on all subsequent caregiver outcomes.

Furthermore, change in caregiver stress (e.g., role overload), which has been found to be more likely to be impacted by change in overall patient behaviors (29;45), was not measured in this study.

Another limitation is this study's reliance on self-report data. While validated clinical assessments were used for measures of patient function, illness and clinical characteristics, patient BPSD was estimated via caregiver report. While this is the case in most caregiving studies due to the fluctuating nature of BPSD, it is certainly plausible that caregiver reports of BPSD may be affected by the caregiver's mental health status. However, our lack of positive findings regarding the impact of change in BPSD parallel to change in caregiver depression suggest that such bias would not have impacted our study conclusions. Similarly, we also relied on caregiver self-report of depressive symptoms. Validated clinical data on caregiver depression and depressive symptoms would have provided greater insight into how caregiver outcomes change over time.

Strengths of this study include a sample of patients with mild dementia who were carefully diagnosed in a consensus conference and well-characterized. Because caregivers were followed beyond patient's nursing home placement, the study design eliminates attrition biases noted in previous studies, in which only caregivers who can adjust to the challenges of daily patient care remain in follow-up studies.(29) Additionally, caregiver data were available on 98% of all patients with caregivers who were alive at the time of study inception. Furthermore, few longitudinal studies of caregiving consider multiple points of follow-up beyond 1-2 years,

thereby compressing analysis of care provision and failing to capture the full spectrum of the prolonged dementia caregiving experience. Finally, instead of only using a cumulative measure of BPSD that includes the wide range of behavioral symptoms (e.g., depression, psychosis, wandering) exhibited by persons with dementia, we examined individual symptom clusters in terms of their impact on subsequent caregiver depression and on change in caregiver depression.

Conclusion

Despite the fact that patients with dementia often, and increasingly, live with their disease for many years such that caregiving is a long-term role, research has not focused on how caregivers respond or adapt to patient BPSD over time. This study finds that there is only a small subset of dementia caregivers who have increasing depressive symptoms over time, but fails to find any connection between individual BPSD that occur in mild dementia or change in BPSD and the course of caregiver depression over time. Such a longitudinal perspective on the dementia patient-caregiver dyad may convey a more complete picture of the impact of BPSD on caregivers than the consistently negative one reported in cross-sectional analyses(5;9-15). Future research should continue to explore the relationship between BPSD symptoms and caregiver outcomes over time. Within caregiving research, the stress process model (31) has been frequently used to conceptualize how stress proliferates from objective burdens (e.g., BPSD) to stress and poor mental health outcomes for caregivers; this model should be expanded to more seriously consider the role of timing and change over time in order to remain instrumental to researchers. A better understanding of the relationship between BPSD and caregiver depressive symptoms over time and how the timing of behaviors across the disease course affect the caregiver will help to inform well-targeted interventions for dementia caregivers.

Table 3.1: Associations between presence of symptom clusters in early dementia and subsequent caregiver depression (n=160)*

	Model 1**		Model 2***		Model 3****	
	OR	95% CI	OR	95% CI	OR	95% CI
Depressive symptoms	.82	.33-2.02	.71	.29-1.76	.79	.33-1.87
Accusatory/aggressive behavior	.94	.44-2.03	.96	.47-1.95	.82	.43-1.54
Non-threatening psychotic behavior	.76	.71-2.43	1.08	.58-2.02	1.03	.57-1.87
Difficult behaviors	1.35	.78-2.32	1.25	.72-2.17	.98	.58-1.67

* multiple time points (mean = 4) included per patient-caregiver dyad

**unadjusted

***adjusted for concurrent patient symptom cluster

****simultaneously adjusted for other concurrent patient symptom clusters, patient functional status, whether caregiver is the spouse

Figure 3.1: Individual trajectories of caregiver depression over time (n=133)

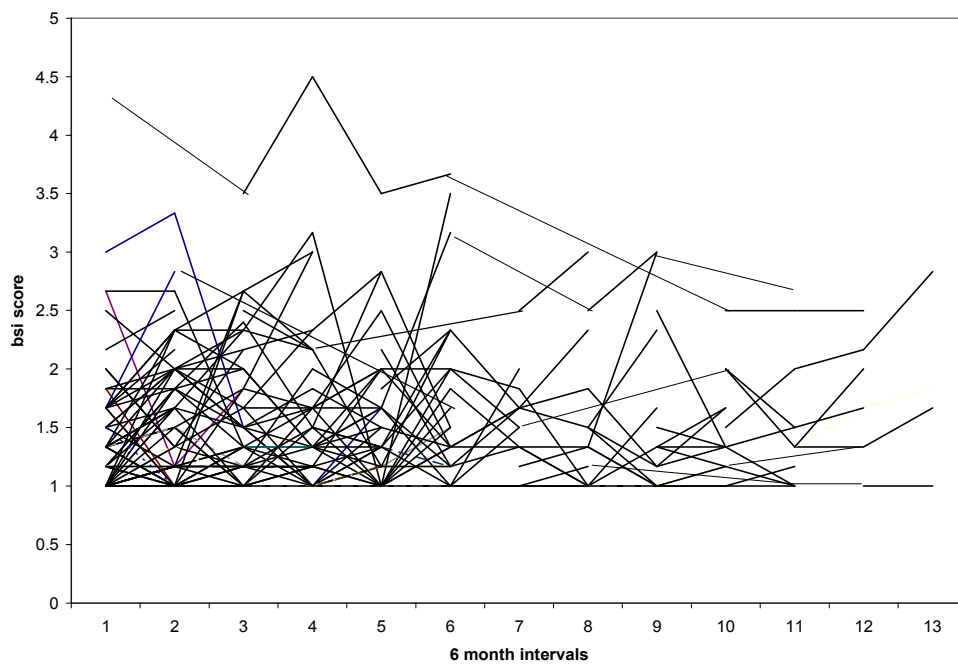


Figure 3.2: Trajectories of caregiver depression over 6 years (n=133)

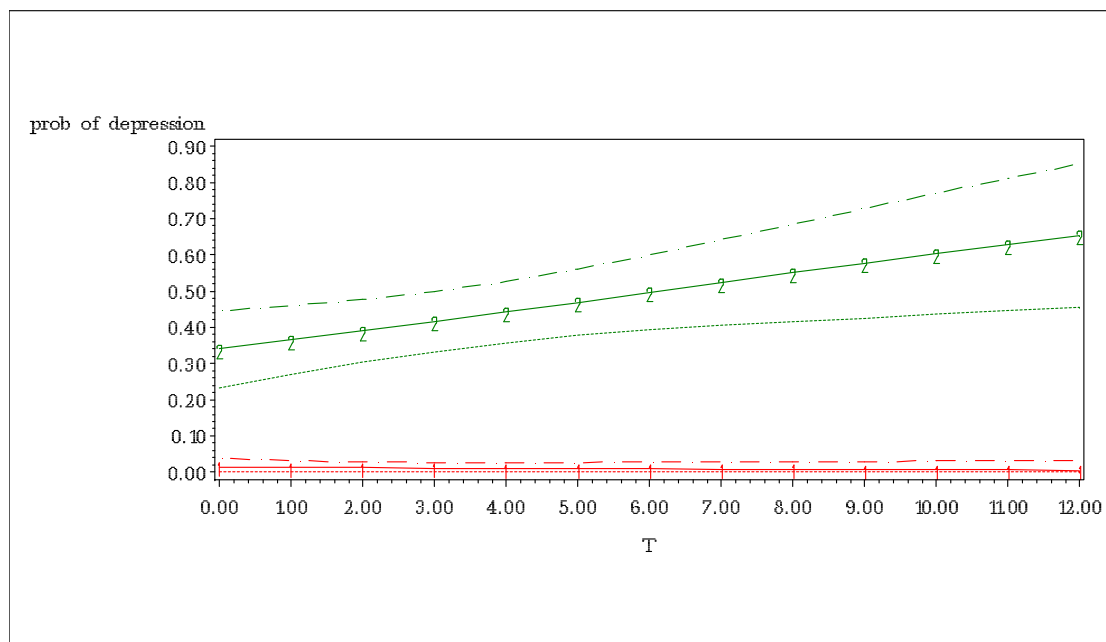


Table 3.2: Model fit for latent class analysis of caregiver depressive symptoms

No. of classes	AIC	BIC	SSABIC
1	-281.5	-286	-284.4
2	-240.3	-251.5	-247.6
3	-239.3	-257.2	-250.9
4	-242.3	-266.9	-258.24

AIC=Akaike information criteria; BIC=Bayesian information criteria; SSABIC=sample size adjusted Bayesian Information Criteria.

Table 3.3: Patient and caregivers characteristics by caregiver depression trajectory class

	Characteristic	categories	Class 1: (n=92) Stable caregivers	Class 2 (n=41) Wear-and- tear caregivers	p- value
Patient mild dementia behaviors	Depressive symptoms	Yes	20%	12.5%	.30
	Accusatory/aggressive behavior	Yes	20.22%	20.55%	.97
	Non-threatening psychotic behavior	Yes	21.11%	22.5%	.86
	Difficult behaviors	Yes	38.2%	46.15%	.40
	Any BPSD	Yes	54.44%	57.5%	.75
Patient demographic and clinical characteristics	Patient age at cohort inception	mean ± SD	75.2	76.78	.25
	Patient gender	female male	63.04% 37.96%	39.02% 60.98%	.01
	Patient ethnicity	white	90.22%	90.44%	.99
	Site	Columbia University	44.57%	51.22%	.76
		Johns Hopkins	23.91%	19.51%	
		Mass General	31.52%	29.27%	
	Diagnosis	Alzheimer's Disease	85.87%	87.8%	.76
		Dementia with Lewy Bodies	14.13%	12.2%	
	Neurologist estimation of duration of illness in years	mean ± SD (range 1-18)	7.57 (3.32)	6.73 (2.7)	.17
	Mini-mental state examination score at study baseline	mean ± SD (range 9-30)	17.59	19.06	.34
Blessed functional activity scale score at study baseline	mean ± SD (range 0-13)	6.95	7.41	.53	
Modified comorbidity index	0	51.14%	52.5%	.89	
	≥1	48.86	47.5%		
Extrapyramidal signs	Yes	14.44%	12.5%	.77	

Caregiver characteristics and activities	Caregiver age at baseline	mean \pm SD	63.67 (13.35)	68.65 (14.47)	.06
	Caregiver gender	female	77.17%	73.17%	.62
	Lives with caregiver at baseline	Yes	54.35%	70.73%	.08
	Relationship to patient	spouse	47.83%	70.83%	.01
	Work at least part-time for pay	Yes	51.25%	33.33%	.07
	Home health aide in last 3 months	Yes	23.46%	31.58%	.35
	Time spent daily with patient	None	2.22%	2.44%	.04
		Up to 3 hrs	35.56%	17.07%	
		3 to 5 hrs	13.33%	9.76%	
	6 to 9 hrs	12.22%	7.32%		
	9 to 12 hrs	8.89%	4.88%		
	More than 12 hrs	27.78%	58.54%		
Assists patient with ADLs	Yes	17.72%	29.73%	.14	

SD=standard deviation; ADLs=Activities of daily living and include bathing, eating; IADLS=Instrumental activities of daily living and include shopping, housekeeping

Figure 3.3: Trajectories of patient depression over 6 years (n=132)

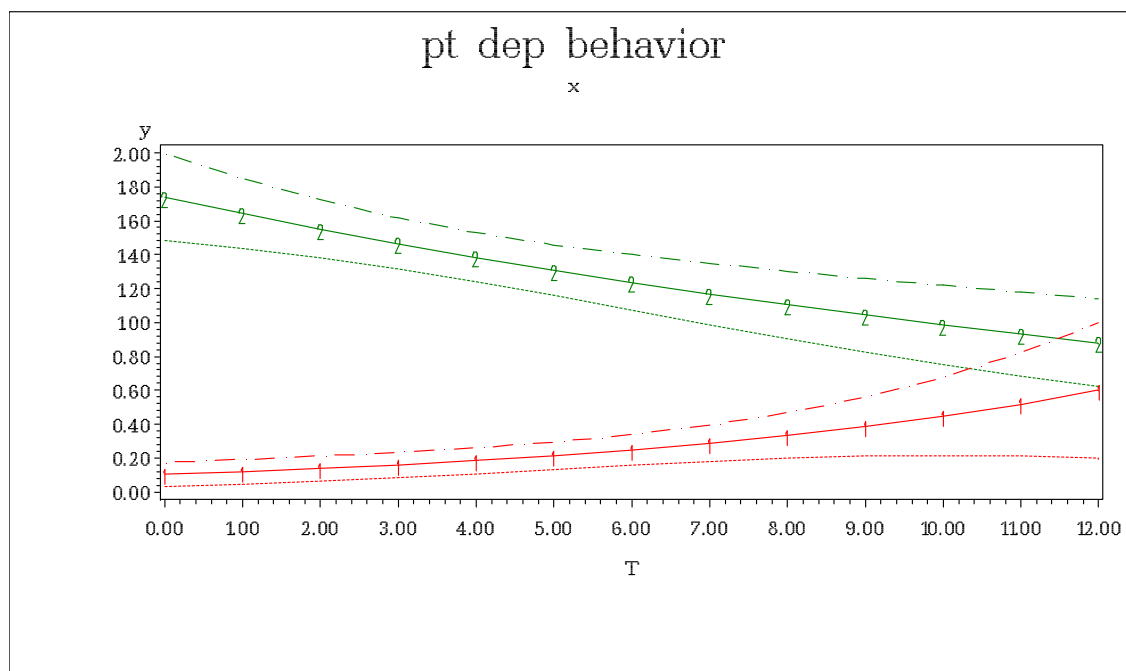


Table 3.4: Patterns of change in patient and caregiver depressive symptoms
(n=132 patient-caregiver dyads)

Patient depression	Caregiver depression	N	%
no change	increase	32	24.24%
no change	no change	30	22.73%
decrease	no change	17	12.88%
decrease	increase	11	8.33%
increase	increase	11	8.33%
no change	decrease	10	7.58%
increase	no change	9	6.82%
decrease	decrease	7	5.30%
increase	decrease	5	3.79%

References

- (1) 2009 Alzheimer's disease facts and figures. *Alzheimers Dement* 2009 May;5:234-270.
- (2) 2010 Alzheimer's Disease facts and figures. Alzheimer's Association; 2010.
- (3) National Alliance for Caregiving, AARP. Caregiving in the U.S. Washington, DC: AARP; 2004.
- (4) Alzheimer's Association and National Alliance for Caregiving. Families care: Alzheimer's disease caregiving in the United States, 2004. 2004.
- (5) Schulz R, O'Brien AT, Bookwala J, Fleissner K. Psychiatric and physical morbidity effects of dementia caregiving: prevalence, correlates, and causes. *Gerontologist* 1995 Dec;35:771-791.
- (6) Pinquart M, Sorensen S. Differences between caregivers and noncaregivers in psychological health and physical health: a meta-analysis. *Psychol Aging* 2003 Jun;18:250-267.
- (7) Aneshensel CS, Pearlin LI, Mullan J.T., Zarit SH, Whitlach C.J. Profiles in caregiving: The unexpected career. San Diego: Academic Press, 1995.
- (8) Cannuscio CC, Jones C, Kawachi I, Colditz GA, Berkman L, Rimm E. Reverberations of family illness: a longitudinal assessment of informal caregiving and mental health status in the Nurses' Health Study. *Am J Public Health* 2002 Aug;92:1305-1311.
- (9) Black W, Almeida OP. A systematic review of the association between the Behavioral and Psychological Symptoms of Dementia and burden of care. *Int Psychogeriatr* 2004 Sep;16:295-315.
- (10) Pinquart M, Sorensen S. Associations of stressors and uplifts of caregiving with caregiver burden and depressive mood: a meta-analysis. *J Gerontol B Psychol Sci Soc Sci* 2003 Mar;58:112-128.
- (11) Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. *Gerontologist* 1980 Dec;20:649-655.
- (12) Clyburn LD, Stones MJ, Hadjistavropoulos T, Tuokko H. Predicting caregiver burden and depression in Alzheimer's disease. *J Gerontol B Psychol Sci Soc Sci* 2000 Jan;55:S2-13.
- (13) Meshefedjian G, McCusker J, Bellavance F, Baumgarten M. Factors associated with symptoms of depression among informal caregivers of demented elders in the community. *The Gerontologist* 1998 Apr;Vol.38:247-253.
- (14) Ballard C, Lowery K, Powell I, O'Brien J, James I. Impact of behavioral and psychological symptoms of dementia on caregivers. *International Psychogeriatrics* 2000;Vol.12:93-105.

- (15) Donaldson C, Tarrier N, Burns A. The impact of the symptoms of dementia on caregivers. *Br J Psychiatry* 1997 Jan;170:62-68.
- (16) Steinberg M, Lyketsos CG. Psychiatric disorders in people with dementia. In Weiner, Myron F (Ed); Lipton, Anne M (Ed). *The American Psychiatric Publishing textbook of Alzheimer disease and other dementias*. (pp. 263-281). Arlington, VA, US: American Psychiatric Publishing, Inc. 2009.
- (17) Steinberg M, Sheppard JM, Tschanz JT, et al. The incidence of mental and behavioral disturbances in dementia: the cache county study. *J Neuropsychiatry Clin Neurosci* 2003;15:340-345.
- (18) Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *JAMA* 2002 Sep 25;288:1475-1483.
- (19) Aalten P, de Vugt ME, Jaspers N, Jolles J, Verhey FR. The course of neuropsychiatric symptoms in dementia. Part I: findings from the two-year longitudinal Maasbed study. *Int J Geriatr Psychiatry* 2005 Jun;20:523-530.
- (20) Sink KM, Covinsky KE, Newcomer R, Yaffe K. Ethnic differences in the prevalence and pattern of dementia-related behaviors. *J Am Geriatr Soc* 2004 Aug;52:1277-1283.
- (21) Donelan K, Hill CA, Hoffman C, et al. Challenged to care: informal caregivers in a changing health system. *Health Aff (Millwood)* 2002 Jul;21:222-231.
- (22) Holtzer R, Tang MX, Devanand DP, et al. Psychopathological features in Alzheimer's disease: course and relationship with cognitive status. *J Am Geriatr Soc* 2003 Jul;51:953-960.
- (23) Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *Int J Epidemiol* 2002 Apr;31:285-293.
- (24) Cottrell LS. The adjustment of the individual to his age and sex roles. *American Sociological Review* 1942;7:617-620.
- (25) Gaugler JE, Zarit SH, Pearlin LI. The onset of dementia caregiving and its longitudinal implications. *Psychol Aging* 2003 Jun;18:171-180.
- (26) Stern Y, Tang MX, Albert MS, et al. Predicting time to nursing home care and death in individuals with Alzheimer disease. *JAMA* 1997 Mar 12;277:806-812.
- (27) Smith GE, Kokmen E, O'Brien PC. Risk factors for nursing home placement in a population-based dementia cohort. *J Am Geriatr Soc* 2000 May;48:519-525.
- (28) Gaugler JE, Kane RL, Newcomer R. Resilience and transitions from dementia caregiving. *J Gerontol B Psychol Sci Soc Sci* 2007 Jan;62:38-44.

- (29) Gaugler JE, Kane RL, Kane RA, Newcomer R. The longitudinal effects of early behavior problems in the dementia caregiving career. *Psychol Aging* 2005 Mar;20:100-116.
- (30) Ballard C, Corbett A, Chitramohan R, Aarsland D. Management of agitation and aggression associated with Alzheimer's disease: controversies and possible solutions. *Curr Opin Psychiatry* 2009 Nov;22:532-540.
- (31) Pearlin LI, Mullan JT, Semple SJ, Skaff MM. Caregiving and the stress process: an overview of concepts and their measures. *Gerontologist* 1990 Oct;30:583-594.
- (32) Townsend A, Noelker L, Deimling G, Bass D. Longitudinal impact of interhousehold caregiving on adult children's mental health. *Psychol Aging* 1989 Dec;4:393-401.
- (33) Alspaugh ME, Stephens MA, Townsend AL, Zarit SH, Greene R. Longitudinal patterns of risk for depression in dementia caregivers: objective and subjective primary stress as predictors. *Psychol Aging* 1999 Mar;14:34-43.
- (34) Goode KT, Haley WE, Roth DL, Ford GR. Predicting longitudinal changes in caregiver physical and mental health: a stress process model. *Health Psychol* 1998 Mar;17:190-198.
- (35) Schulz R, Williamson GM. A 2-year longitudinal study of depression among Alzheimer's caregivers. *Psychol Aging* 1991 Dec;6:569-578.
- (36) Aneshensel CS, Botticello AL, Yamamoto-Mitani N. When caregiving ends: the course of depressive symptoms after bereavement. *J Health Soc Behav* 2004 Dec;45:422-440.
- (37) Zhang B, Mitchell SL, Bambauer KZ, Jones R, Prigerson HG. Depressive symptom trajectories and associated risks among bereaved Alzheimer disease caregivers. *Am J Geriatr Psychiatry* 2008 Feb;16:145-155.
- (38) Garre-Olmo J, Lopez-Pousa S, Vilalta-Franch J, de Gracia BM, Vilarrasa AB. Grouping and trajectories of the neuropsychiatric symptoms in patients with Alzheimer's disease, part I: symptom clusters. *J Alzheimers Dis* 2010;22:1157-1167.
- (39) Garre-Olmo J, Lopez-Pousa S, Vilalta-Franch J, de Gracia BM, Vilarrasa AB. Grouping and trajectories of neuropsychiatric symptoms in patients with Alzheimer's disease. Part II: two-year patient trajectories. *J Alzheimers Dis* 2010;22:1169-1180.
- (40) Mittelman MS, Roth DL, Haley WE, Zarit SH. Effects of a caregiver intervention on negative caregiver appraisals of behavior problems in patients with Alzheimer's disease: results of a randomized trial. *J Gerontol B Psychol Sci Soc Sci* 2004 Jan;59:27-34.
- (41) Baumgarten M, Hanley JA, Infante-Rivard C, Battista RN, Becker R, Gauthier S. Health of family members caring for elderly persons with dementia. A longitudinal study. *Ann Intern Med* 1994 Jan 15;120:126-132.

- (42) Hooker K, Bowman SR, Coehlo DP, et al. Behavioral change in persons with dementia: relationships with mental and physical health of caregivers. *J Gerontol B Psychol Sci Soc Sci* 2002 Sep;57:453-460.
- (43) Caron W, Boss P, Mortimer J. Family boundary ambiguity predicts Alzheimer's outcomes. *Psychiatry* 1999;62:347-356.
- (44) Danhauer SC, McCann JJ, Gilley DW, Beckett LA, Bienias JL, Evans DA. Do behavioral disturbances in persons with Alzheimer's disease predict caregiver depression over time? *Psychol Aging* 2004 Mar;19:198-202.
- (45) Gaugler JE, Davey A, Pearlin LI, Zarit SH. Modeling caregiver adaptation over time: the longitudinal impact of behavior problems. *Psychol Aging* 2000 Sep;15:437-450.
- (46) Grafstrom M, Winblad B. Family burden in the care of the demented and nondemented elderly--a longitudinal study. *Alzheimer Dis Assoc Disord* 1995;9:78-86.
- (47) Li LW, Seltzer MM, Greenberg JS. Change in depressive symptoms among daughter caregivers: an 18-month longitudinal study. *Psychol Aging* 1999 Jun;14:206-219.
- (48) Fauth EB, Zarit SH, Femia EE, Hofer SM, Stephens MA. Behavioral and psychological symptoms of dementia and caregivers' stress appraisals: intra-individual stability and change over short-term observations. *Aging Ment Health* 2006 Nov;10:563-573.
- (49) Neundorfer MM, McClendon MJ, Smyth KA, Stuckey JC, Strauss ME, Patterson MB. A longitudinal study of the relationship between levels of depression among persons with Alzheimer's disease and levels of depression among their family caregivers. *J Gerontol B Psychol Sci Soc Sci* 2001 Sep;56:301-313.
- (50) Ornstein KA. The differential impact of unique BPSD for the dementia caregiver: How and why do patients' individual symptom clusters impact caregiver depressive symptoms? 2011.
- (51) Stern Y, Folstein M, Albert M, et al. Multicenter study of predictors of disease course in Alzheimer disease (the "predictors study"). I. Study design, cohort description, and intersite comparisons. *Alzheimer Dis Assoc Disord* 1993;7:3-21.
- (52) McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984 Jul;34:939-944.
- (53) Stern Y, Sano M, Paulson J, Mayeux R. Modified Mini-Mental State Examination: validity and reliability. *Neurology* 1987;37:179.
- (54) Folstein MF, Folstein SE, McHugh PR. Mini mental state: A practical state for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-198.

- (55) McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* 1996 Nov;47:1113-1124.
- (56) Bollen K, Curran P. *Latent Curve Models: A Structural Equation Perspective* Wiley Interscience, 2005.
- (57) Derogatis L. *The Brief Symptom Inventory (BSI): Administration, scoring and procedures manual*, 3rd ed. Minneapolis, MN: NCS Pearson, 1993.
- (58) Nunnally J, Bernstein I. *Psychometric Theory*, 3rd ed. New York: McGraw Hill, 1994.
- (59) Devanand DP, Miller L, Richards M, et al. The Columbia University Scale for Psychopathology in Alzheimer's disease. *Arch Neurol* 1992 Apr;49:371-376.
- (60) Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry* 1968 Jul;114:797-811.
- (61) Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-383.
- (62) Marcus R, Marder K, Bell K, Dooneief G, Mayeux R, Stern Y. Interrater Reliability of Extrapyrmidal Signs in a Group Assessed for Dementia. *Arch Neurol* 1991;48:1147-1149.
- (63) Scarmeas N, Hadjigeorgiou GM, Papadimitriou A, et al. Motor signs during the course of Alzheimer disease. *Neurology* 2004 Sep 28;63:975-982.
- (64) Jones B, Nagin DS, Roeder K. A SAS Procedure Based on Mixture Models for Estimating Developmental Trajectories. *Sociological Methods Research* 2001;29:374-393.
- (65) Nagin DS, Tremblay RE. Analyzing developmental trajectories of distinct but related behaviors: a group-based method. *Psychol Methods* 2001 Mar;6:18-34.
- (66) Nagin DS. Analyzing developmental trajectories: A semiparametric . group-based approach. *Psychol Methods* 1999;4:139-157.
- (67) Yee JL, Schulz R. Gender differences in psychiatric morbidity among family caregivers: a review and analysis. *Gerontologist* 2000 Apr;40:147-164.
- (68) Pinquart M, Sorensen S. Gender differences in caregiver stressors, social resources, and health: an updated meta-analysis. *J Gerontol B Psychol Sci Soc Sci* 2006 Jan;61:33-45.
- (69) Muthen BO, Khoo ST. Longitudinal studies of achievement growth using latent variable modeling. *Learning and Individual Differences* 1998;10:73-101.
- (70) Lopez-Pintado S, Romo J. On the concept of depth for functional data. *J Am Stat Assoc* 2009;104:486-503.

- (71) Yao F, Müller HG, Wang JL. Functional data analysis for sparse longitudinal data. *J Am Stat Assoc* 2005;100:577-590.
- (72) Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R. Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA* 1994 Apr 6;271:1004-1010.

Conclusion

Given the growth in the number of elderly in the United States and worldwide with dementia, we need to develop more strategies to assist family members who face the chronic stress and consequent negative mental health outcomes of caring for patients for ever increasing time periods. While the literature has uncovered the critical role BPSD play,(1;2) if and why specific behaviors negatively impacts the caregiver and how the timing of these behaviors matter over the course of the caregiving relationship, has not been previously elucidated. Determining whether there are specific behaviors that differentially impact caregivers and testing the causal mechanisms by which these relationships occur as well as how these relationships may change over time, can be useful for developing more focused and effective interventions for patients and caregivers. This dissertation explicitly sought to fill this research gap by utilizing a longitudinal study of mild dementia patients with detailed repeated assessments of BPSD to test the impact of individual symptom clusters (depressive symptoms, accusatory/aggressive symptoms, non-threatening psychotic symptoms, and difficult to manage behaviors) on caregiver depression. In this conclusion we synthesize the findings presented in Chapters 1, 2, and 3 with the aims of not only summarizing the conclusions from this dissertation as a whole, but also reflecting on our overall findings, offering public health implications, and suggesting future research directions.

Summary of findings

In chapter 1, via a systematic lit review we examined existing caregiving literature to determine which individual symptoms exert negative impact on caregivers. We also sought to identify causal mechanisms studied and gaps in the literature regarding how timing affects these relationships. We found that despite the significant amount of research conducted examining BPSD and caregiving, the literature focused on the aggregate effect of these symptoms rather than on the effect of individual symptoms. Furthermore, existing studies categorized BPSD

based on how they clinically manifest in the patient, rather than from the perspective of how they may differentially impact the caregiver. We concluded that future research requires the re-conceptualization of BPSD from the perspective of their impact on the caregiver to examine hypothesis-driven differences among BPSD symptom clusters. Additionally, further investigation of the impact of timing as well as the role of dementia illness stage on the patient behavior and caregiver outcome relationship is warranted.

In chapter 2 we aimed to move this research forward by testing the differential impact of symptom clusters on caregiver depression. While we hypothesized that accusatory and aggressive symptoms would result in more depression for caregivers than other symptoms, we did not find this to be the case. All clusters exerted small effects on caregiver depression, with patient depressive symptoms exerting the strongest and most consistently stable relationship with caregiver depression. While we did not find large differences in effect sizes between the clusters examined, data indicate that specific symptom clusters, i.e., patient depression, may be driving the BPSD-caregiver depression relationship, and should be further examined. We also concluded that the patient depression-caregiver depression relationship was mediated by both perceived burden to caregivers and impact of symptoms on the patient. These findings suggest that we need to consider different pathways beyond subjective stress by which BPSD may result in negative health effects for caregivers.

We extended this work in chapter 3 to explore the timing of patient depressive symptoms and other individual BPSD as they relate to caregiver outcomes. We did not find evidence that the presence of individual BPSD at mild dementia impacted subsequent caregiver depressive symptoms. When examining change patterns over time, we found that most caregivers had stable trajectories of depressive symptoms, with a smaller subset showing more evidence for

wear-and-tear over time. Furthermore, there was no evidence in our study for an association between change in patient depressive symptoms and change in caregiver depressive symptoms.

Implications of the findings

The strength of this dissertation is our novel focus on determining which specific components of the larger BPSD construct are so detrimental for caregivers and looking at symptom clusters from the perspective of how they may impact caregivers. Over the course of dementia, BPSD occur in the vast majority of patients with dementia.(3-9) Because symptoms are pervasive when aggregated, increasing specificity within the larger BPSD construct will ultimately result in more targeted interventions for caregivers as well as treatment protocols for patients. This may be especially important as we do not yet have effective means for controlling most BPSD,(10-13) nor do we have standardized interventions in place with positive lasting effects on caregiver mental health.(14;15)

Our examination of the impact of individual BPSD, although not conclusive, suggests that there may be particular symptoms or behaviors that especially impact negative caregiver outcomes. We did not find, as hypothesized, that accusatory and aggressive behaviors were driving the relationship between BPSD and caregiver depression. We did find, however, that patient depression was consistently associated with caregiver depression after controlling for other symptom clusters, whereas difficult behaviors (e.g., wandering, sundowning) had smaller effects that were not significant. Unfortunately, definitive implications from this study as to the differential impact of patient depressive symptoms on caregiver depression would be premature given that all clusters tested had a similar range of small effect sizes, and that this question of differentiating symptoms has never before been tested so rigorously.

We found that the relationship between individual BPSD and caregiver depression was mediated by how the behavior actually impacted the caregiver's functioning in addition to the caregiver's subjective stress. While caregiver burden has been previously shown to mediate the relationship between patient objective behavior and caregiver depression,(16-18) the role of impact on patient functioning in the causal pathway has not been explored. Our findings suggest that caregivers recognize the difficulty that depressive symptoms may cause for the patients who experience them and that this mechanism may also result in negative caregiver outcomes such as depression. Unfortunately, because we did not find very different effect sizes among clusters, we were unable to test causal mechanisms by which some symptoms exerted more influence than others. This new finding that the patient experience of the symptom mediates the BPSD-caregiver depression relationship, similar to research that has examined the patient suffering pathway,(19;20) suggests we may need to take a different approach for caregiver intervention. Specifically, in addition to focusing on respite care or skills training for caregivers, interventions can minimize impact of symptoms for the patient, thus helping the caregiver to cope with the effects of the symptoms and suffering experience of the patient.

Overall, we found that most caregivers had stable and minimal depressive symptoms over time, although we did identify a group of caregivers who had increased depression over time ("wear-and-tear caregivers"). While most work on caregivers over long periods of time estimates one overall trajectory for caregiver symptoms, these findings suggest it may be more useful to identify disparate trajectories among caregivers to target those caregivers at greater risk for poor long-term outcomes. Our findings also suggest that by examining patient behaviors and caregiver outcomes longitudinally, we gain a more complete perspective on the patient-caregiver dyad than when they are examined at one point in time. While we found a clear relationship

between patient depression and caregiver depression cross-sectionally, we did not find any relationship between change in patient depression and change in caregiver depression.

Future directions

Our examination of existing literature on individual BPSD and caregiving found that BPSD have only been conceptualized and categorized based on how they manifest within patients. We believe that researchers interested in caregiver outcomes should begin to focus more on the caregiver's perspective on symptoms instead of grouping symptoms together clinically using similar domains used for non-dementia patients (e.g., psychotic vs. mood symptoms) or based on how they empirically cluster within the dementia patient. If the ultimate goal is to alleviate caregiver stress and depression then we must continue to try to determine if there are key ingredients in BPSD that are particularly problematic for caregivers and how they work. By categorizing behaviors based on manifestation in dementia patients, or even less informative, based on how they are associated among non-demented psychiatric patients, we may never be able to capture the specific elements that are critical for caregivers.

While our study did not find large differences in effect sizes between individual symptom clusters, our data suggests that individual symptom clusters, i.e., depression, may differentially impact caregivers. We believe that researchers should continue to examine patient behaviors from this perspective and to focus on understanding why specific symptoms may differentially impact caregivers. Given that clinicians cannot realistically control all BPSD in patients, and that we do not have the infrastructure to provide respite care and psychosocial support to all distressed caregivers, targeted efforts to improve the well-being of the dementia caregiver are

necessary. Only through understanding the mechanisms by which symptoms exert negative effects can we improve our currently mediocre prevention and treatment efforts.

We hypothesized in chapter 2 that because aggressive psychotic behaviors may be unexpected, difficult to ignore and more frightening to caregivers, they may have greater impact on depression in caregivers. While we did not find this to be the case in our sample, we hope future research will continue to examine this hypothesis in other datasets. In particular, this hypothesis should be examined relative to other measures of caregiver depression (including clinical measures) as well as other negative caregiver outcomes including increased burden and declines in physical health. Furthermore, we relied in this study upon regrouping an existing measure of BPSD designed to assess patient clinical psychopathology (e.g., hallucinations) to create four ‘caregiver-impacting’ patient symptom clusters (e.g., non-threatening psychotic behaviors). Future work may benefit from directly measuring symptoms based on how they impact the caregivers (e.g., *does the patient engage in behaviors that are threatening to you?*) to better test this hypothesis.

Caregiving is, and will continue to be, a long-term role. Researchers should therefore approach caregiving from a long-term perspective when they consider caregiver health outcomes and intervention approaches. In order to develop effective interventions for dementia caregivers, understanding the dynamic relationship between patient symptoms and caregiver depression and critically examining the role of timing of behaviors, is necessary. Our work has only begun to ask important questions about the impact of individual BPSD over time by focusing on change in patient depressive symptoms. Although we did not find relationships when examining timing of behaviors and change in caregiver depression over time, given the scarce research to date, we believe that future research should continue to explore the relationship between BPSD symptoms

and caregiver outcomes over time. In particular, future work should continue to study how other individual BPSD impact caregiver outcomes over time, especially given that we found a distinct group of caregivers who had increased depressive symptoms over time. Additionally, we recommend examining the role of critical transitions (e.g., nursing home placement, symptom development) that may have long-term consequences for caregiver outcomes. Furthermore, while our data did not find an association between early dementia symptoms and subsequent caregiver outcomes, we are hesitant to conclude that BPSD that occur in mild dementia do not independently impact caregiver depression given lack of research. Similarly, while we examined behaviors that occur early in dementia on subsequent outcomes, there may be other sensitive time periods in the course of dementia that should also be examined. For example, it is possible that we need to examine the occurrence of BPSD over the entire first year of diagnosis or at another critical juncture in the patient-caregiver relationship, perhaps at certain thresholds of cognitive or functional decline.

While our data confirms existing work that finds a strong cross-sectional association between the occurrence of patient depression and caregiver depression, we did not find this association to exist when we examined the relationship between change in patient depression relative and change in caregiver depression. This may be due to the fact that we did not capture the correct time lag in our modeling as we examined overall change in behaviors over several year intervals. The impact of patient depressive behaviors on caregiver depression may be more instantaneous. Future work may consider more detailed modeling of time lags between patient behaviors and caregiver outcomes to better elucidate this complex relationship.

This work also suggests that we may need to move beyond the stress process model, which has heretofore guided most dementia caregiving research, to conceptualize the patient-caregiver

dyad. According to the stress process model,(21;22) caregiving is a chronic stressor that gives rise to strains from multiple domains and ultimately leads to increased risk for psychiatric distress and diagnosable disorder. The model differentiates between the objective, more concrete stressors (e.g., BPSD, functional dependence or cognitive impairment), the caregiver's subjective experience (or appraisal) of those stressors, and background and contextual factors (e.g., education, living situation, age) which impact the stressor and caregiver outcomes. While our research supports this conceptual framework, our findings suggest that this model needs to be expanded in future research to (1) consider alternative pathways by which objective stressors may impact outcomes (e.g., via perceived impact on patient) and (2) incorporate a long-term perspective that considers both sensitive time periods in the patient-caregiving relationship and how stressors change over time.

Finally, while this work is based on a study of dementia patient-caregiver dyads, we believe our findings apply to other types of patients and caregivers. Testing patient behaviors from the perspective of how they impact caregivers may be a useful strategy for caregiving research if we are ultimately interested in improving the health and well-being of caregivers. A long-term perspective is essential for all types of caregiving in which patient behaviors and caregiver response change over time. Relationships regarding sensitive time periods or change over time should be hypothesized and tested. Long-term dyadic relationships should be conceptualized and studied not merely as snapshots in time, but, rather, as long-term relationships which have the possibility of changing over time.

Conclusion

This dissertation furthered our understanding of the well-studied relationship between BPSD and caregiver depression by focusing on individual symptom clusters and timing of behaviors over the patient-caregiver relationship. This work has summarized what is known about individual BPSD and caregiving and adds to our understanding of the BPSD and caregiving relationship by asking: *Which behaviors are most difficult for caregivers? Why is this so? When is it so?* Our findings suggest that individual symptoms may have differential effects on caregivers and may impact caregivers not just through subjective stress, but also because of the impact the symptoms have on the patients themselves. We also find further evidence for the stability in caregiver depression over time, although there may be caregivers who continue to decline over time. We hope this work can spark further research examining the differential impact between symptom clusters and can steer research agendas away from simply grouping together all symptoms, or examining them based on clinical manifestations. Furthermore, we hope to see continued work that examines BPSD and their impact on the patient-caregiver relationship over time.

References

- (1) Black W, Almeida OP. A systematic review of the association between the Behavioral and Psychological Symptoms of Dementia and burden of care. *Int Psychogeriatr* 2004 Sep;16:295-315.
- (2) Ballard C, Lowery K, Powell I, O'Brien J, James I. Impact of behavioral and psychological symptoms of dementia on caregivers. *International Psychogeriatrics* 2000;Vol.12:93-105.
- (3) Steinberg M, Sheppard JM, Tschanz JT, et al. The incidence of mental and behavioral disturbances in dementia: the cache county study. *J Neuropsychiatry Clin Neurosci* 2003;15:340-345.
- (4) Steinberg M, Lyketsos CG. Psychiatric disorders in people with dementia. In Weiner, Myron F (Ed); Lipton, Anne M (Ed). *The American Psychiatric Publishing textbook of Alzheimer disease and other dementias*. (pp. 263-281). Arlington, VA, US: American Psychiatric Publishing, Inc. 2009.
- (5) Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *JAMA* 2002 Sep 25;288:1475-1483.
- (6) Aalten P, de Vugt ME, Jaspers N, Jolles J, Verhey FR. The course of neuropsychiatric symptoms in dementia. Part I: findings from the two-year longitudinal Maasbed study. *Int J Geriatr Psychiatry* 2005 Jun;20:523-530.
- (7) Tariot PN, Mack JL, Patterson MB, et al. The Behavior Rating Scale for Dementia of the Consortium to Establish a Registry for Alzheimer's Disease. The Behavioral Pathology Committee of the Consortium to Establish a Registry for Alzheimer's Disease. *Am J Psychiatry* 1995 Sep;152:1349-1357.
- (8) Sink KM, Covinsky KE, Newcomer R, Yaffe K. Ethnic differences in the prevalence and pattern of dementia-related behaviors. *J Am Geriatr Soc* 2004 Aug;52:1277-1283.
- (9) Torti FM, Jr., Gwyther LP, Reed SD, Friedman JY, Schulman KA. A multinational review of recent trends and reports in dementia caregiver burden. *Alzheimer Dis Assoc Disord* 2004 Apr;18:99-109.
- (10) Yaffe K. Treatment of neuropsychiatric symptoms in patients with dementia. *The New England Journal of Medicine* 2007 Oct;Vol.357:1441-1443.
- (11) Cohen-Mansfield J. Nonpharmacologic interventions for inappropriate behaviors in dementia: a review, summary, and critique. *Am J Geriatr Psychiatry* 2001;9:361-381.
- (12) Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. *JAMA* 2005 Feb 2;293:596-608.

- (13) Ayalon L, Gum AM, Feliciano L, Arean PA. Effectiveness of nonpharmacological interventions for the management of neuropsychiatric symptoms in patients with dementia: a systematic review. *Arch Intern Med* 2006 Nov 13;166:2182-2188.
- (14) Pinquart M, Sorensen S. Helping caregivers of persons with dementia: which interventions work and how large are their effects? *Int Psychogeriatr* 2006 Dec;18:577-595.
- (15) Mittelman MS. Psychosocial intervention research: challenges, strategies and measurement issues. *Aging Ment Health* 2008 Jan;12:1-4.
- (16) Hooker K, Bowman SR, Coehlo DP, et al. Behavioral change in persons with dementia: relationships with mental and physical health of caregivers. *J Gerontol B Psychol Sci Soc Sci* 2002 Sep;57:453-460.
- (17) Son J, Erno A, Shea DG, Femia EE, Zarit SH, Stephens MA. The caregiver stress process and health outcomes. *J Aging Health* 2007 Dec;19:871-887.
- (18) Goode KT, Haley WE, Roth DL, Ford GR. Predicting longitudinal changes in caregiver physical and mental health: a stress process model. *Health Psychol* 1998 Mar;17:190-198.
- (19) Monin JK, Schulz R. Interpersonal effects of suffering in older adult caregiving relationships. *Psychol Aging* 2009 Sep;24:681-695.
- (20) Schulz R, McGinnis KA, Zhang S, et al. Dementia patient suffering and caregiver depression. *Alzheimer Dis Assoc Disord* 2008 Apr;22:170-176.
- (21) Pearlin LI, Mullan JT, Semple SJ, Skaff MM. Caregiving and the stress process: an overview of concepts and their measures. *Gerontologist* 1990 Oct;30:583-594.
- (22) Aneshensel CS, Pearlin LI, Mullan J.T., Zarit SH, Whitlach C.J. Profiles in caregiving: The unexpected career. San Diego: Academic Press, 1995.

Methodological Appendices

Appendix 1.A: Categorization techniques for symptoms in literature review

For the vast majority of studies reviewed, we retained the original categorizations schemas used by the authors when categorizing which symptoms/symptom clusters were tested. However, in the following cases, we re-categorized symptoms, combined symptoms into one category, or subdivided symptoms in order to be able to synthesize findings across the 35 studies reviewed.

1. “demanding behavior” and “difficult behavior” were combined into one category: “demanding/difficult behavior”
2. “disinhibition” and “acting out” were combined into one category: “disinhibition/acting out”
3. “dysphoria” categorized as “depression”
4. “non-aggressive agitation” categorized as “agitation”
5. “mood-related depression” categorized as “depression”
6. “physical aggression” categorized as “aggression”
7. “repetitive questions” categorized as “repetitive behavior”
8. “aggression/agitation” a single category within the Neuropsychiatric Inventory, was separated into two subcomponents: “aggression” and “agitation”
9. “behavioral disturbances” were subdivided into their subcomponents (as described by the authors): “activity disturbances” and “aggression”

Appendix 2.A: The Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD)

In this paper we used the CUSPAD to assess patient BPSD. The CUSPAD is a semi-structured rating scale that a clinician or research assistant administers to the informant regarding the presence of 26 patient symptoms during the last month before each interview.

1. Delusions (past month)

General

In the past month, has the patient talked about any strange ideas or unusual beliefs? No 0
Yes 1

If "Yes", can you describe them for me? _____

Was this the case some of the time or most of the time? Persistent 0
Transient 1
N/A 2

Will the patient accept the truth if corrected? No 0
Yes 1
N/A 2

Paranoid delusions (past month)

(a) Has the patient felt that others are stealing things from him/her? No 0
Yes 1

Was this the case some of the time or most of the time? Persistent 0
Transient 1
N/A 2

Will the patient accept the truth if corrected? No 0
Yes 1
N/A 2

(b) Has the patient suspected that his/her wife/husband is unfaithful? No 0
[Circle N/A if patient is single or widowed.] Yes 1
N/A 2

Was this the case some of the time or most of the time?	Persistent 0 Transient 1 N/A 2
Will the patient accept the truth if corrected?	No 0 Yes 1 N/A 2
(c) Has the patient had any other unfounded suspicions?	No 0 Yes 1

If "Yes", can you describe them? _____

Was this the case some of the time or most of the time?	Persistent 0 Transient 1 N/A 2
Will the patient accept the truth if corrected?	No 0 Yes 1 N/A 2

Global Severity Rating for Paranoid Delusions:

To what extent would you say these behaviors have affected the *patient's* daily activities and functioning?

- 0 No effect
- 1 Minimal effect
- 2 Mild effect
- 3 Moderate effect
- 4 Severe effect
- 9 Not applicable

How difficult or disturbing do *you* find these behaviors to manage or deal with?

- 0 No difficulty
- 1 Minimally difficult

- 2 Mildly difficult
- 3 Moderately difficult
- 4 Extremely difficult
- 9 Not applicable

Delusions of Abandonment (past month)

Has the patient suspected or accused the caregiver of plotting to leave him/her?	No	0
	Yes	1
Was this the case some of the time or most of the time?	Persistent	0
	Transient	1
	N/A	2
Will the patient accept the truth if corrected?	No	0
	Yes	1
	N/A	2

Somatic delusions (past month)

Has the patient had any false beliefs that he/she has cancer or another physical illness?	No	0
	Yes	1
Was this the case some of the time or most of the time?	Persistent	0
	Transient	1
	N/A	2
Will the patient accept the truth if corrected?	No	0
	Yes	1
	N/A	2

Misidentification syndromes (past month)

(a) Has the patient stated that people are in the house/home when nobody is there?	No	0
	Yes	1
Was this the case some of the time or most of the time?	Persistent	0
	Transient	1
	N/A	2
Will the patient accept the truth if corrected?	No	0

	Yes	1
	N/A	2
(b) Has the patient looked into the mirror and said it is someone else?	No	0
	Yes	1
Was this the case some of the time or most of the time?	Persistent	0
	Transient	1
	N/A	2
Will the patient accept the truth if corrected?	No	0
	Yes	1
	N/A	2
(c) Has the patient misidentified people, for example, said that the spouse/caregiver is an imposter?	No	0
	Yes	1
Was this the case some of the time or most of the time?	Persistent	0
	Transient	1
	N/A	2
Will the patient accept the truth if corrected?	No	0
	Yes	1
	N/A	2
(d) Has the patient said that his/her house or home is not his/her home?	No	0
	Yes	1
Was this the case some of the time or most of the time?	Persistent	0
	Transient	1
	N/A	2
Will the patient accept the truth if corrected?	No	0
	Yes	1
	N/A	2
(e) Has the patient believed that the characters on television are real or in the room? [circle N/A if the patient has no access to a television]	No	0
	Yes	1
	N/A	2
Was this the case some of the time or most of the time?	Persistent	0
	Transient	1
	N/A	2

Will the patient accept the truth if corrected? No 0
Yes 1
N/A 2

Global Severity Rating for Misidentification Delusions:

To what extent would you say these behaviors have affected the *patient's* daily activities and functioning?

0 No effect
1 Minimal effect
2 Mild effect
3 Moderate effect
4 Severe effect
9 Not applicable

How difficult or disturbing do *you* find these behaviors to manage or deal with?

0 No difficulty
1 Minimally difficult
2 Mildly difficult
3 Moderately difficult
4 Extremely difficult
9 Not applicable

Other delusions (past month)

Has the patient had any false beliefs or other strange ideas that I have not
not asked you about? No 0
Yes 1

If "Yes", can you describe them? _____

Was this the case some of the time or most of the time?
Persistent 0
Transient 1
N/A 2

Will the patient accept the truth if corrected?

No 0

Yes 1

N/A 2

2. Hallucinations (past month)

(a) Has the patient heard voices or sounds when no one is there? [Auditory]

No

0

Yes: Vague 1

Clear 2

If "yes", can you describe them? _____

(b) Has the patient seen visions? [Visual]

No

0

Yes: Vague 1

Clear 2

If "Yes", can you describe them? _____

(c) Has the patient reported unusual smells like burning rubber, gas or rotten eggs?

No

0

[Olfactory]

Yes:

Vague 1

Clear 2

If "Yes", can you describe them? _____

(d) Has the patient felt that things are crawling under his/her skin? [Tactile]

No 0

Yes: Vague 1

Clear 2

If "Yes", can you describe them? _____

(e) Has the patient reported any other hallucinations?

No 0 Yes: Vague 1
Clear 2

If "Yes", can you describe them? _____

Global Severity Rating for Hallucinations:

To what extent would you say these behaviors have affected the *patient's* daily activities and functioning?

- 0 No effect
- 1 Minimal effect
- 2 Mild effect
- 3 Moderate effect
- 4 Severe effect
- 9 Not applicable

How difficult or disturbing do *you* find these behaviors to manage or deal with?

- 0 No difficulty
- 1 Minimally difficult
- 2 Mildly difficult
- 3 Moderately difficult
- 4 Extremely difficult
- 9 Not applicable

3. Illusions (past month)

Has the patient reported that one thing is something else, for example,
saying that a pillow looks like a person or a light bulb looks like a fire starting?

No 0
Yes:
Vague 1
Clear 2

If "Yes", can you describe them? _____

Global Severity Rating for Illusions:

To what extent would you say these behaviors have affected the *patient's* daily activities and functioning?

- 0 No effect
- 1 Minimal effect
- 2 Mild effect
- 3 Moderate effect
- 4 Severe effect
- 9 Not applicable

How difficult or disturbing do *you* find these behaviors to manage or deal with?

- 0 No difficulty
- 1 Minimally difficult
- 2 Mildly difficult
- 3 Moderately difficult
- 4 Extremely difficult
- 9 Not applicable

4. Behavioral Disturbances (past month)

- (a) Has the patient wandered away from home or from the caregiver? No
0
Yes 1
- (b) Has the patient made verbal outbursts? No
0
Yes 1
- (c) Has the patient used physical threats and/or violence? No
0
Threatening behavior 1
Physical violence 2
- (d) Has the patient shown agitation or restlessness? No
0
Yes 1
- (e) Has the patient been more confused at night or during evening, compared to the day? No
0
Yes 1

Global Severity Rating for Behavioral Disturbances:

To what extent would you say these behaviors have affected the *patient's* daily activities and functioning?

- | | |
|---|-----------------|
| 0 | No effect |
| 1 | Minimal effect |
| 2 | Mild effect |
| 3 | Moderate effect |
| 4 | Severe effect |
| 9 | Not applicable |

How difficult or disturbing do *you* find these behaviors to manage or deal with?

- | | |
|---|----------------------|
| 0 | No difficulty |
| 1 | Minimally difficult |
| 2 | Mildly difficult |
| 3 | Moderately difficult |
| 4 | Extremely difficult |
| 9 | Not applicable |

5. Depression (past month)

If the answer to items (a) to (c) below is "Yes", circle the appropriate level of severity.

If the answer is "No", circle "N/A".

- | | |
|---|-------|
| (a) Has the patient been sad, depressed, blue or down in the dumps? | No |
| | 0 |
| | Yes 1 |

If "Yes", how do you know they are sad, e.g. do they cry or complain that they feel sad?

Write down details: _____

Was he/she depressed:

- | | |
|------------------|---|
| N/A | 0 |
| occasionally | 1 |
| some of the time | 2 |
| most of the time | 3 |
| all of the time | 4 |

(b) Has the patient had difficulty sleeping? No 0
Yes 1

If "Yes", is there: N/A 0
slight difficulty 1
at least 2 hours sleep at night 2
less than 2 hours sleep at night 3
excessive sleep/sleepiness 4

(c) Has the patient's appetite changed? No 0
Yes 1

If "Yes", circle one: N/A 0
slightly decreased 1
No appetite. Food is tasteless 2
Need persuasion to eat at all 3
excessive appetite 4

Global Severity Rating for Depression:

To what extent would you say these behaviors have affected the *patient's* daily activities and functioning?

- 0 No effect
- 1 Minimal effect
- 2 Mild effect
- 3 Moderate effect
- 4 Severe effect
- 9 Not applicable

How difficult or disturbing do *you* find these behaviors to manage or deal with?

- 0 No difficulty
- 1 Minimally difficult
- 2 Mildly difficult
- 3 Moderately difficult
- 4 Extremely difficult
- 9 Not applicable

Appendix 2.B: Creation of individual BPSD symptom clusters

Below we describe in detail the creation of four individual BPSD symptom clusters based on the CUSPAD (see Appendix 2.A):

1. Accusatory and aggressive symptoms

We constructed a dichotomous variable based on the presence of one or more of six items that measure paranoid and abandonment delusions as well as aggression.

I. Paranoid delusions

- A. people are stealing things
- B. unfaithful wife/husband
- C. other unfounded suspicions

II. Abandonment delusions

- A. accusing caregiver of plotting to leave him/her

III. Aggression

- A. threatening behavior
- B. physical violence

2. Non-threatening psychotic symptoms:

We constructed a dichotomous variable to indicate the presence of any non-threatening psychotic symptoms. This will be based on report of exhibiting one or more of the 13 items that constitute the remainder of the psychotic symptoms measured in the CUSPAD which include hallucinations, illusions, misidentification delusions and somatic delusions.

I. Somatic delusions

- A. the patient has cancer or other physical illness

II. Misidentification delusions

- A. people are in the house when nobody is there
- B. someone else is in the mirror
- C. spouse/caregiver is an imposter
- D. the patient's house is not his/her home

- E. the characters on television are real
- F. other false beliefs or strange ideas

III. Hallucinations

- A. heard voices when no one is there
- B. seen visions
- C. reported unusual smells like burning rubber, gas, or rotten eggs
- D. felt that things are crawling under his/her skin
- E. other hallucinations

IV. Illusions

- A. reported that one thing is something else, for example, saying that a pillow looked like a person or light bulb looked like a fire starting

3. Depressive symptoms:

We constructed a dichotomous variable to indicate whether patients have depressive symptoms

based on their answering yes to the following:

- I. Has the patient been sad, depressed, blue or down in the dumps?

and

- II. Reporting at least one of the following items:

- A. the patient had difficulty sleeping
- B. the patient's appetite changed.

4. Difficult to manage behaviors:

The presence of difficult to manage behaviors was dichotomized based on the presence of one or

more of the following four behaviors:

- A. wandering away from home or from the caregiver
- B. showing agitation or restlessness
- C. making verbal outbursts
- D. sundowning (increased disorientation, restlessness, agitation in the late afternoon or evening)

Appendix 2C: Analysis of individual BPSD-caregiver depression relationship adjusting for anti-depressant and neuroleptic use

After testing the relationship between each individual BPSD symptom cluster and caregiver depression in fully adjusted models, we further controlled for concurrent antidepressant and neuroleptic use which were also found to be associated with caregiver depression. All patient/caregiver report of prescription and over the counter (OTC) medication use was recorded at each visit on a medication acquisition form. A neurologist who specializes in dementia categorized all prescription medications into 18 categories including neuroleptics and antidepressants. For each drug category, a dichotomous variable indicating whether a patient reported using any medications in that drug category at each visit was constructed. As shown in the table below, the small and statistically significant effect of patient depressive symptoms remained after controlling for these two medication types. The general pattern of small, non-statistically significant, effect size estimates remain the same for all BPSD tested.

Association between BPSD and caregiver depression*

BPSD symptom cluster	OR	95% CI
Depressive symptoms	1.79	1.26-2.45
Non-threatening psychotic behavior	1.21	0.76-1.91
Accusatory/aggressive	1.21	0.79-1.86
Difficult behaviors	1.01	0.62-1.64

* simultaneously adjusted for other symptom clusters, patient functional status, patient relationship to caregiver, and patient antidepressant or neuroleptic use

Appendix 2.D: Alternative (sensitivity) analysis of individual BPSD-caregiver depression relationship treating outcome as continuous variable

In order to support our findings regarding the differential effect of depressive symptoms relative to other BPSD, we conducted additional tests of the relationship between individual symptom clusters using a continuous measure of caregiver depression. Because the data were right skewed we used a Poisson GEE model. The table below gives estimates for each individual symptom cluster while simultaneously adjusting for other patient symptom clusters, patient functional status and whether caregiver is the spouse. The effect estimate for the effect of depressive symptoms in the adjusted Poisson model is .09. By exponentiating this value we determine that the ratio of mean caregiver depression for depressed patients compared to non-depressed patients is 1.09. The effect estimate for the effect of non-threatening psychotic symptoms in the adjusted Poisson model is .07. By exponentiating this value we determine that the ratio of mean caregiver depression for patients who exhibit non-threatening psychotic symptoms compared to patients who do not exhibit these symptoms is 1.07. While the other symptoms have similar sizes and direction, they are not statistically significant. Similar to what was shown using logistic regression, depressive symptoms continue to have weak but statistically significant effects. However, in this model, the effect of depressive symptoms appear less differentiated from other individual symptoms.

Association between BPSD and caregiver depression using Poisson regression

BPSD symptom cluster	Ratio of mean caregiver depression scores	Estimate (95% CI)	p-value
Depressive symptoms	1.09	.09 (.03-.16)	.007
Non-threatening psychotic behavior	1.07	.07 (.02-.14)	.014
Accusatory/aggressive	1.04	.04 (-.03-.10)	.312
Difficult behaviors	1.03	.03 (-.04-.11)	.370

Appendix 2.E: Alternative (sensitivity) analysis of individual BPSD-caregiver depression relationship treating individual symptoms as continuous variables

Continuous measures of each symptom cluster were created as follows:

1. Accusatory and aggressive symptoms : We created a scale (range=0-6) representing the presence of up to six of the following behaviors. A score of 0 represents no behaviors and a score of 6 indicates the presence of all behaviors.

- people are stealing things
- unfaithful wife/husband
- other unfounded suspicions
- accusing caregiver of plotting to leave him/her
- threatening behavior
- physical violence

2. Non-threatening psychotic symptoms: We created a scale (range=0-13) representing the presence of up to 13 of the following behaviors. A score of 0 represents no behaviors and a score of 13 indicates the presence of all behaviors.

- the patient has cancer or other physical illness
- people are in the house when nobody is there
- someone else is in the mirror
- spouse/caregiver is an imposter
- the patient's house is not his/her home
- the characters on television are real
- other false beliefs or strange ideas
- heard voices when no one is there
- seen visions
- reported unusual smells like burning rubber, gas, or rotten eggs
- felt that things are crawling under his/her skin
- other hallucinations
- reported that one thing is something else

3. Depressive symptoms: A score for patient depression (range=0-4) based on overall depressed mood, presence of other depressed symptoms (difficulty sleeping, change in appetite) and frequency of depressed mood (more than occasionally).

4. Difficult to manage behaviors: We created a scale (range=0-4) representing the presence of up to four of the following behaviors. A score of 0 represents no behaviors and a score of 4 indicates the presence of all behaviors.

- wandering away from home or from the caregiver
- showing agitation or restlessness
- making verbal outbursts
- sundowning (increased disorientation, restlessness, agitation in the late afternoon or evening)

We conducted additional tests of the relationship between individual symptom clusters and caregiver depression using continuous measures of each symptom clusters using logistic GEE models to see if we could better support our findings as to the differential effect of patient depressive symptoms. The table below gives estimates for each individual symptom cluster while simultaneously adjusting for other patient symptom clusters, patient functional status and whether caregiver is the spouse. Again, depressive symptoms have the strongest effect, and remain statistically significant, although other symptom clusters also have similar effect sizes.

Association between individual BPSD and caregiver depression

BPSD symptom cluster	OR	95% CI
Depressive symptoms	1.15	1.03-1.28
Accusatory/aggressive behavior	1.00	.84-1.20
Non-threatening psychotic behavior	1.03	.94-1.13
Difficult behaviors	1.12	.93-1.35

Appendix 2.F: Equality constraints to test differential impact of patient depressive symptoms

In order to formally test the significance of apparent different effect sizes between depressive symptoms and other BPSD symptom clusters, we compared two logistic models. In the first model we allowed for a unique estimate of the regression coefficient for patient depression while constraining the effects of other symptoms by forming a composite measure summing the other three behavior symptoms (model 1: $y = \beta_1(\text{patient depression}) + \beta_2(\text{accusatory/aggressive symptoms} + \text{non-threatening symptoms} + \text{difficult behaviors})$). In the second model all four symptom measures were added to form a composite measures, therefore assigning the same common regression coefficient to each symptom measure (model 2: $y = \beta_1(\text{patient depression} + \text{accusatory/aggressive symptoms} + \text{non-threatening symptoms} + \text{difficult behaviors})$). Thus in model 1 the regression coefficient for patient depressive symptoms is allowed to vary whereas in model 2 the regression coefficient is constrained to a common value. We used a logistic model and included continuous measures of individual variables which were standardized using z-scores. We compared the differences in the likelihood ratio chi-square statistics for the two models. This value is distributed as chi-square, with degree of freedom (DOF) equal to the number of restrictions.

Comparison of restricted and unrestricted models

	Chi-Square	DOF
Model 1: unrestricted	13.195	2
Model 2: restricted	8.5196	1

Difference=4.68 > 3.77

The model 1 chi-square values are significantly higher ($p < .05$) than the model 2 values suggesting that patient depressive symptoms have different effects on caregiver depression than other symptom clusters.

Appendix 2.G: Symptom cluster correlations

In order to determine whether the observed differential impact of depressive symptoms above other BPSD was due to higher correlations among other clusters, we examined correlations between four symptom clusters. The table below represents the Pearson correlation coefficients and p-values across symptom clusters

Correlations among individual BPSD

	Non-threatening psychotic behavior	Aggressive/accusatory symptoms	Depression	Difficult behaviors
Non-threatening psychotic behavior	1	.26 <.0001	.12 .0014	.16 <.0001
Aggressive/accusatory symptoms		1	.15 <.0001	.28 .0003
Depression			1	.17 .0006
Difficult behaviors				1

As expected, all are significantly correlated ranging from .12 (depression and non-threatening behavior) to .28 (difficult behaviors and aggressive/accusatory symptoms).

In order to test how correlation between symptom clusters impacted our findings, we tested the effects of each cluster without adjusting for other clusters. After adjusting for known confounding factors (functional status and caregiver relationship) but no other symptom clusters, difficult behaviors remained unassociated with outcome (OR=1.20; 95% CI=0.80 -1.70).

Depression remains the strongest and only significant effect estimate even without controlling for other symptom clusters, suggesting that correlation between clusters is not responsible for depression having strongest and most significant effect estimate. As shown in the table below, the patterns for relative effect sizes and statistical significance remain in the full model (model 2)

which simultaneously adjusts for concurrent symptom clusters and model 1, which does not adjust for concurrent symptom clusters.

Comparison of effect of individual BPSD symptom clusters whether or not adjusting for concurrent symptom clusters

	Model 1*		Model 2**	
	OR	95% CI	OR	95% CI
Non-threatening psychotic behavior	1.55	1.08-2.22	1.39	0.93-2.08
Aggressive/accusatory symptoms	1.41	1.02-1.95	1.17	0.82-1.69
Depression	1.70	1.25-2.33	1.55	1.14-2.11
Difficult behaviors	1.20	0.80 -1.70	1.03	0.67-1.58

*adjusting for patient functional status and whether caregiver is spouse

** simultaneously adjusted for other patient symptom clusters, patient functional status, whether caregiver is the spouse

Furthermore, because aggression and non-threatening behavior were highly correlated symptom clusters with borderline statistically significant effect estimates, we specifically looked at the effect of each one in the presence and the absence of the other. As shown below, the patterns remain the same whether or not the ‘correlated’ symptom is included in the model.

Comparison of effect of non-threatening and aggressive behavior whether or not adjusting for concurrent symptom clusters

	Model 1*		Model 2**		Model 3***	
	OR	95% CI	OR	95% CI	OR	95% CI
Non-threatening psychotic behavior	1.76	1.22-2.53	1.45	.99-2.12	1.40	.94-2.07
Aggressive/accusatory symptoms	1.42	0.99-2.01	1.31	.93-1.83	1.18	.83-1.68

*unadjusted

**adjusting for patient functional status, whether caregiver is spouse, and patient depression

***adjusting for patient functional status, whether caregiver is spouse, patient depression, and non-threatening psychotic behavior or aggressive/accusatory symptoms

Appendix 2.H: Analysis of psychotic symptoms and caregiver depression

Contrary to our hypothesis, we did not find a strong association between accusatory/aggressive symptoms and caregiver depression. Yet we did find a consistently small, although not statistically significant ($p < .05$) effect, between this cluster as well as non-threatening psychotic symptoms in our analyses. We therefore did further exploratory analyses of the association between psychotic symptoms in general and caregiver depression to determine how clustering of psychotic symptoms impacted our findings.

First, we subdivided the accusatory/aggressive symptom cluster to examine the individual association between (1) accusatory symptoms and (2) aggressive symptoms with caregiver depression.

Effects of individual psychotic symptoms on caregiver depression

symptom cluster	Model 1*		Model 2**	
	OR	95% CI	OR	95% CI
Accusatory symptoms	1.31	.90-1.81	1.16	.81-1.67
Aggression	1.57	.98-2.52	1.11	.66-1.86

* unadjusted

** adjusted for other symptom clusters, whether the caregiver is the patient's spouse and patient functional status.

We continued to find small effect sizes with confidence intervals including the null value using this re-categorization, thus suggesting that the combination of these symptom types were not masking any true effect in our main analysis.

We next re-categorized psychotic symptoms based on their clinical classifications as hallucinations and delusions (because illusions were only reported by <3% of patients they were not included) to determine how they impact caregiver depression.

Effects of clinically classified symptom clusters on caregiver depression

Clinically classified symptom cluster	OR	95% CI
Hallucinations	1.08	0.73-1.60
Delusions	1.50	1.02-2.19

*adjusted for other symptom clusters, whether the caregiver is the patient's spouse and patient functional status.

Similarly, we continued to find small effects, with little differentiation. Next we examined the relationship between the presence of any type of patient psychotic symptom and caregiver depression in a multivariate analysis.

Effects of any clinically classified symptom cluster on caregiver depression

Clinically classified symptom cluster	OR	95% CI
Any psychotic symptom	1.59	1.08-2.37

* adjusted for non-psychotic symptom clusters, whether the caregiver is the patient's spouse and patient functional status.

Psychotic symptoms as a whole impacted caregiver depression, suggesting that we may want to consider other categorizations of psychotic symptoms in future analyses to capture their impact on caregivers.

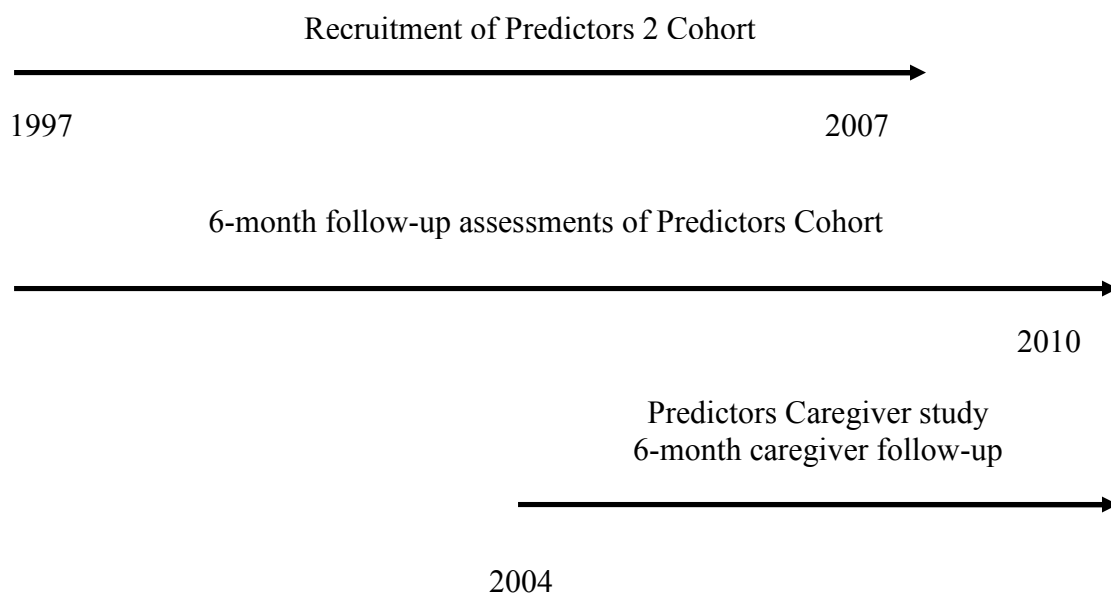
Appendix 2.I: Analysis of individual symptoms and caregiver depression among AD patients only

Because our study sample includes patients with AD and DLB, we originally planned to test whether the effects of individual BPSD were different for those patients with AD compared to those with DLB. However, due to the few number of cases with DLB (n=22) we were unable to test this interaction. Below we examined the effects of individual BPSD symptoms on caregiver depression among patients with AD only in fully adjusted models. As shown below, our general patterns of findings remain unchanged when we examined patients with AD only.

Associations between symptom clusters and caregiver depression among AD patients

	OR	95% CI
Depressive symptoms	1.49	1.06-2.09
Accusatory/aggressive behavior	1.15	0.77-1.73
Non-threatening psychotic behavior	1.51	0.98-2.31
Difficult behaviors	1.17	0.73-1.87

*simultaneously adjusted for other patient symptom clusters, patient functional status, whether caregiver is the spouse in logistic GEE model

Appendix 3.A Diagram of Predictors 2 cohort and Predictors Caregiver study

Appendix 3.B: Association between presence of any BPSD in early dementia and caregiver depression

In addition to examining the effect of individual BPSD clusters on caregiver depression in early dementia, we also examined the effect of the presence of any BPSD on subsequent caregiver dementia. Any BPSD were examined (1) as a dichotomous variable (yes= presence of any of the four symptom clusters tested; no= all symptom clusters absent) and (2) as an ordinal variable (range=0-4) indicating the number of individual symptom clusters present at baseline. Each variable was tested using GEE logistic models. As shown below, no relationship was found between the presence of early BPSD and subsequent caregiver depressive symptoms using either BPSD measure.

Association between any early BPSD and caregiver depression

	Model 1*		Model 2**	
	OR	95% CI	OR	95% CI
Any BPSD (dichotomous)	1.41	.83-2.40	1.14	.67-1.94

* unadjusted

** adjusted for whether the caregiver is the patient's spouse and patient functional status.

Association between any early BPSD and caregiver depression

	Model 1*		Model 2**	
	OR	95% CI	OR	95% CI
Any BPSD (range 0-4)	1.07	.85-1.34	.97	.76-1.25

* unadjusted

** adjusted for whether the caregiver is the patient's spouse and patient functional status.