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Dementia Risk in Elders with Anxiety and Insomnia

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Dementia Risk in Elders with Anxiety and Insomnia

by

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Dedication

To my parents, Dave and Dian Wallis, for their relentless support and often irrational faith in me. To my father, for not giving up on me when I took wrong turns. To my mother, for unending support and instilling the love of math.

To my wife, Sharon, and sons, Oliver and Simon, for giving me the motivation to keep going. To my wife, for her patience, support, and for seeing my potential.

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Dementia Risk in Elders with Anxiety and Insomnia

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Current evidence suggests that there is an association between benzodiazepine-receptor-agonist medications (BZRA) and subsequent dementia. Expert opinions differ regarding whether the association indicates a causal relationship. There is sufficient evidence that neuropsychiatric symptoms, such as anxiety and insomnia, are indicators of prodromal dementia which may lead to treatment with benzodiazepine-receptor agonist medications. Therefore, the association between BZRAs and subsequent dementia may be a spurious correlation for which the prodromal onset is responsible. This study proposed to test the postulate that the anxiety and insomnia symptom cluster (A/I) is a predictor of dementia.

A retrospective data analysis was conducted on the Aging, Demographics, and Memory Study (ADAMS) dataset in order to determine whether A/I symptoms or treatment were associated with subsequent dementia or cognitive impairment (DOCI). The study controlled for gender and comorbid depression. The study excluded BZRA usage and medical comorbidities that were either confounding variables in assessment or alternative explanations of cognitive decline. The study used chi-square analysis, comparison of incidence rates, odds ratios, relative risk, and logistic regression to investigate the idea that the A/I symptom cluster indicates developing prodromal dementia.

The study failed to find an association between A/I symptoms and subsequent DOCI in the total sample. However, there was a significant relationship between A/I symptoms and subsequent DOCI in the male gender that was not found in females. No association was found for the A/I medications in any of the analyses. Further investigation of the ADAMS dataset without removing the exclusion variables also showed that BZRA usage was not associated with subsequent DOCI.

The gender differences identified suggest prodromal dementia phenotypes that are differentially expressed in males and females. The lack of association between A/I medications and subsequent DOCI in this study is validated by the lack of association between BZRA medications and subsequent DOCI in the larger ADAMS dataset. While it is unlikely that a single reliable predictor of subsequent dementia exists, by triangulating the approaches between multiple disciplines—such as biomarkers and neurological studies—with neuropsychiatric manifestations of prodromal dementia, it is possible that reliable early prediction may be accomplished. Earlier identification would then lead to effective treatments and ultimately prevention.

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List of Abbreviations

ADAMS	Aging, Demographics, and Memory Study
A/I	Anxiety and/or Insomnia
BZRA	Benzodiazepine-receptor-agonist medications
χ^2	Chi square statistic
CIND	Cognitive impairment but not demented
CI	Confidence Interval
DOCI	Dementia or cognitive impairment
HRS	Health and Retirement Study
IR	Incidence Rate
IRR	Incidence Rate Ratio
LBD	Lewy Body Dementia
NPI	Neuropsychiatric Inventory
OR	Odds Ratio
RR	Relative Risk
SD	Standard Deviation

CHAPTER 1

Introduction

STATEMENT OF THE PROBLEM

Dementia is a global problem and a significant cause of disability around the world (Rizzi, Rosset, & Roriz-Cruz, 2014). The World Health Organization (WHO, 2016) estimates that 47.5 million people currently have dementia worldwide, with this number projected to reach 135.5 million in the next 35 years. While Ferencz and Gerritsen (2015) reported an average of 5-7% incidence of dementia for individuals over age 60, Rizzi et al. (2014) cited global variations from 2.3-14%, with reports greater than 20% in the Middle East. In the United States, the 2012 incidence of dementia was 8.8%, according to a recent report on data from the Health and Retirement Study (Langa et al., 2017). Although there is some evidence that the incidence that the prevalence of dementia is declining (Langa et al., 2017; Satizabal et al., 2016)—likely due to improvements in the early identification and treatment of cardiovascular and cerebrovascular disease—WHO (2016) estimates the global economic burden of dementia in 2010 was $600 billion.

Given the aging of the huge baby-boomer generation, interest in addressing the causes of dementia has grown in tandem. In addition to identifying the underlying etiology of the condition, there have been growing concerns regarding the possibility that medications used to treat other comorbidities might be responsible for increased risk for dementia and Alzheimer's disease. In 2014, the British Medical Journal published a study by Billioti de Gage et al. that reported BZRAs—a class of medications used for their anticonvulsant and muscle relaxant properties, in addition to treating symptoms of anxiety and insomnia (Baldwin et al., 2013; Olfson, King, & Schoenbaum, 2015)—were found to be associated with an increased risk of Alzheimer's disease and warned that "Unwarranted

long term use of these drugs should be considered as a public health concern" (p. 1). The next year, the authors published a review of the evidence and estimated that there was an increased risk of dementia of 1.5 – 2 times with the use of benzodiazepines (Billioti de Gage, Pariente, & Bégaud, 2015).

This produced a notable reaction among the media with various publications and news reports touting titles such as “Severe Collateral Damage” (Reuther, 2015), "Benzodiazepine use increases Alzheimer's risk" (Rosenberg, 2015), “New study links common prescription drugs to Alzheimer's disease” (Crealy, 2014), and “Anxiety medications may be tied to Alzheimer's risk” (Norton, 2014). News website The Australian warned that “Doctors should take extra care when considering prescribing sleeping pills for elderly patients” ("Sedative chronic use linked to Alzheimer's," 2014).

The concern was not limited to the popular press. Professional publications used the articles as evidence that the clinical practice of prescribing BZRA medications posed concerning risks and must change (Kolar & Kolar, 2016; Martin, Tamblyn, Ahmed, Benedetti, & Tannenbaum, 2015; Reuther, 2015; Kristine Yaffe & Boustani, 2014). Tannenbaum (2015) stated that “Recent research about chronic benzodiazepine therapy leading to an increased risk of Alzheimer disease prompts a discussion about benzodiazepine cessation” (p. E27). Some experts in the field, such as Salzman and Shader (2015), questioned the interpretation that the correlation suggested causation.

BACKGROUND AND SIGNIFICANCE

The American Geriatric Society (AGS, 2015) includes all BZRAs among the medications that it strongly recommends avoiding in elders due to increased risk of falls, automobile accidents, and confusion. Yet, BZRA prescriptions in the United States increase with age, with 7.4% of 51-64 year-olds and 8.7% of 65-80 year-olds receiving a BZRA (Olfson et al., 2015). Because all BZRA medications are regulated as schedule IV controlled substances by the DEA (2011), and for the other reasons like fall risk (AGS,

2015), they are not first-line treatments of A/I in older adults (Mulsant & Pollock, 2015). However, their use for other conditions that are not considered prodromal indicators—such as muscle spasms, tremors, and seizures—poses challenges to untangling their contribution to risk for dementia.

In addition, while current evidence from three recent meta-analyses suggested a correlation between benzodiazepine receptor agonist usage and subsequent dementia diagnosis (Bellou et al., 2016; Billioti de Gage et al., 2015; Zhong, Wang, Zhang, & Zhao, 2015), there has been parallel acknowledgement that correlation is not causation. Pariente, Billioti de Gage, Moore, and Bégaud (2016) discussed theoretical mechanisms for BZRA medications contributing to dementia pathology, but these mechanisms have not been validated. Rather than BZRAs being a causal agent, a viable alternative explanation proposes the existence of a dementia prodrome.

A *prodrome* is the period of time before an individual meets full diagnostic criteria for a syndrome (Beaudreau, Fairchild, Spira, Lazzeroni, & O'Hara, 2013). A dementia prodrome that includes symptoms of anxiety and insomnia may necessitate treatment that commonly includes BZRA medications. In this case, the correlation between BZRA usage and subsequent dementia is a secondary effect that actually highlights treatment of this prodrome (Salzman & Shader, 2015). Therefore, the correlation could be seen as evidence that anxiety and insomnia are prodromal symptoms of dementia (Balon, Fava, & Rickels, 2015; Coyle-Gilchrist, Peck, & Rowe, 2012; Salzman & Shader, 2015). Recent studies by Imfeld et al. (2015) and Gray et al. (2016) found that the association between BZRAs and subsequent dementia is lower with longer usage of BZRAs. This suggests that new onset neuropsychiatric symptoms may reflect prodromal symptoms of dementia rather than a causal relationship between BZRA usage and subsequent dementia. Additionally, it is possible that treating neurodegenerative pathology exerts a protective or preventative effect.

The search for prodromal indicators is not new. Multiple studies have looked into various groups of neuropsychiatric symptoms as prodromal indicators of dementia (Forrester, Gallo, Smith, & Leoutsakos, 2016; Geda et al., 2014; Pink et al., 2015), while other studies have looked at specific symptoms such as anxiety (de Bruijn et al., 2014; Gulpers et al., 2016; Petkus et al., 2016) and insomnia (J. C. Chen et al., 2016; Hahn, Wang, Andel, & Fratiglioni, 2014; Kabeshita et al., 2016; K. Yaffe, Nettiksimmons, Yesavage, & Byers, 2015). Cognitive impairment but not demented (CIND) and mild cognitive impairment (MCI) precede dementia, and neuropsychiatric symptoms have been shown to increase the likelihood of conversion to dementia (Beaudreau et al., 2013; Cooper, Sommerlad, Lyketsos, & Livingston, 2015).

If anxiety and insomnia (A/I) are the prodromal symptoms that BZRAs treat, then a major confound in determining the risk of BZRA usage is posed by including individuals with comorbid anxiety and insomnia disorders. No studies have specifically looked at the A/I symptom cluster that BZRA medications treat. In addition, previous studies have not adequately controlled for comorbid anxiety, insomnia, or the alternative treatments for these conditions. However, it is unlikely that an elder would have used a BZRA for anxiety or insomnia without also having tried a first-line medication; hence, it is possible to explore the linkage between A/I and dementia by eliminating those with BZRA treatments. If BZRA medication usage identifies prodromal dementia symptoms and predicts dementia, then A/I symptoms and non-BZRA treatments for A/I should also predict dementia.

ANALYTIC FRAMEWORK

To assess the predictive relationship over time between A/I symptoms and dementia without the influence of BZRA medications, it was necessary to identify a longitudinal database with the relevant clinical variables. To that end, this study is a retrospective data analysis of the Aging, Demographics, and Memory Study (ADAMS, 2007) dataset—sponsored by the National Institute of Aging (grant number NIA U01AG009740)—a

supplement to the Health and Retirement Study (HRS). The study follows the previous works of Beaudreau et al. (2013) exploring the relationships between neuropsychiatric symptoms and risk of mild cognitive impairment and dementia; Billioti de Gage et al. (2014) on benzodiazepines and risk of dementia; Amieva et al. (2008) and their 14 year study of prodromal Alzheimer's dementia; Petkus et al. (2016) on anxiety and dementia risk in twins; and the recommendations for future study by Billioti de Gage et al. (2015) and Salzman and Shader (2015).

The study by Beaudreau et al. (2013) served as the analytic framework for the study. The authors used a series of logistic regression analyses to evaluate the relationships between variables on the Neuropsychiatric Inventory (NPI), apolipoprotein E epsilon 4 allele (APOEε4; a high risk variant of the APOE gene highly associated with Alzheimer's disease), and progression to cognitive impairment in the ADAMS dataset. Beaudreau et al. also used the ADAMS database but did not include the final wave of the ADAMS study in their analyses and did not utilize the new onset qualifier for symptoms on the NPI. Whereas Beaudreau et al. used the cumulative score for the NPI, this study only used scores for the A/I symptom cluster with the new-onset or worsened symptom specifier.

DEFINITION OF RELEVANT TERMS

This study used the following terms:

Dementia is a disorder of cognitive functioning that causes progressive declines in memory, thought, behavior, and functional ability (WHO, 2016). Social and emotional changes often accompany the cognitive decline.

Cognitive impairment but not demented (CIND) refers to cognitive decline that does not meet diagnostic criteria for dementia (Plassman et al., 2008).

A *prodrome* is the period of time before an individual meets full diagnostic criteria for a syndrome (Beaudreau et al., 2013). Symptoms during this time may be indications of sub-syndromal manifestations of a progressive illness.

Prodromal symptoms are the manifestations of symptoms during the prodrome of an illness (Amieva et al., 2008).

Neuropsychiatric symptoms are observed changes in behavior, emotion, cognition, or otherwise that are presumed manifestations of neurological changes (Belleville, Fouquet, Duchesne, Collins, & Hudon, 2014). Neuropsychiatric symptoms of developing dementia have been identified to manifest for several years before cognitive decline.

Anxiety is "an abnormal and overwhelming sense of apprehension and fear often marked by physical signs (such as tension, sweating, and increased pulse rate), by doubt concerning the reality and nature of the threat, and by self-doubt about one's capacity to cope with it" ("Anxiety," n.d.).

Insomnia is a "prolonged and usually abnormal inability to get enough sleep" ("Insomnia," n.d.).

Benzodiazepine-receptor-agonist (BZRA) medications are medications that agonize the function of gamma-aminobutyric acid-A ($GABA_A$) receptors on inhibitory GABA interneurons in the amygdala by binding to the benzodiazepine site on the $GABA_A$ receptor (Stahl, 2013). Although the binding site was named after the benzodiazepine class of medications, other non-benzodiazepine medications also bind to the benzodiazepine receptor site. For this reason, the term BZRA was used to include all of the medications that share this mechanism of action.

Anxiety and insomnia medications are medications that are used to treat anxiety and/or insomnia. The lists of these medications—obtained from Stahl (2014)—include significant overlap that prevents the separate analyses of these groups.

Elders and *old age* are relative terms that describe the interval variable age. For this study, these terms refer to the age of the sample used by the ADAMS, which included participants at least 70 years old with a mean age of 77 (University of Michigan, 2007).

SPECIFIC AIMS

Neuropsychiatric manifestations of developing dementia are likely present at least 2-5 years prior to the diagnosis of dementia (Belleville et al., 2014). If this dementia prodrome causes elders to seek treatment for anxiety and insomnia, then there should be an association with subsequent dementia for all treatments for anxiety and insomnia in elders, not just BZRAs. This study looked specifically at the symptom cluster treated by BZRA medications and the other medication treatments for those symptoms. The purpose of this study was to explore the possibility that new-onset or worsened A/I symptoms in elders predicts dementia or cognitive impairment (DOCI). This study's primary focus is on early identification of an unfortunate disease and not on the practice prescribing of BZRAs in elders.

Specific Aim 1

Evaluate the association between A/I symptoms and subsequent DOCI among participants in the Aging, Demographics, and Memory Study (ADAMS).

RESEARCH QUESTION 1.1

Do cognitively normal individuals with A/I symptoms in Wave A have an increased incidence of DOCI in Waves C or D in comparison to those that did not have A/I symptoms in Wave A?

RESEARCH QUESTION 1.2

Do cognitively normal individuals with anxiety, insomnia, and depressive (A/I/D) symptoms in Wave A have an increased incidence of DOCI in Waves C or D in comparison to those that did not have A/I/D symptoms in Wave A?

Specific Aim 2

Evaluate the association between non-BZRA anxiolytic medications or sleep aids (A/I medications) and subsequent DOCI among participants in the ADAMS.

RESEARCH QUESTION 2.1

Do cognitively normal individuals that reported using A/I medications in Wave A have an increased incidence of DOCI in Waves C or D in comparison to those that did not report using A/I medications in Wave A?

Specific Aim 3

Evaluate the association between anxiety, depressive, and insomnia symptoms, the usage of A/I medications, and subsequent DOCI among participants of the ADAMS.

RESEARCH QUESTION 3.1

What is the best set of predictors (A/I medication usage, A/I/D symptoms, gender) from Wave A of developing DOCI in Wave C or D?

CHAPTER 2

Review of Literature

BENZODIAZEPINE-RECEPTOR-AGONIST MEDICATIONS AND DEMENTIA RISK

This section summarizes the current state of evidence for the relationship between BZRA medications and subsequent dementia.

Reviews

Three recent systematic and meta-analytic reviews (Bellou et al., 2016; Billioti de Gage et al., 2015; Zhong et al., 2015) have provided evidence for a correlation between benzodiazepine usage and subsequent dementia. All three reviews acknowledge that the correlation may be evidence of prodromal symptoms that these medications treat rather than evidence of a causal relationship. While incorporating many of the same pool of studies, each review addressed a different goal and perspective; the following sections describe these reviews.

FRANCE 2015

Billioti de Gage et al. (2015) summarized the previous studies demonstrating that a correlation between benzodiazepine receptor agonist (BZRA) usage and subsequent diagnosis of dementia. Fastbom, Forsell, and Winblad (1998) were the first to demonstrate a correlation between benzodiazepine usage and subsequent dementia. From 2002-2014 there were eight case-controlled and cohort studies (Billioti de Gage et al., 2012; Billioti de Gage et al., 2014; P.-L. Chen, Lee, Sun, Oyang, & Fuh, 2012; Gallacher et al., 2012; R. Lagnaoui et al., 2002; Rajaa Lagnaoui et al., 2009; C. S. Wu, Ting, Wang, Chang, & Lin, 2011; C. S. Wu, Wang, Chang, & Lin, 2009) that identified a link between benzodiazepine usage and subsequent dementia. The French group more recently published an article

clarifying that the mechanism for the association between BZRA medications and subsequent DOCI is unclear and may be the result of treatment for prodromal symptoms of dementia (Pariente et al., 2016).

CHINA 2015

Zhong et al. (2015) completed a meta-analysis on six studies between 2002 and 2014 that evaluated the relationship between benzodiazepine usage and dementia; the combined sample size was 45,391. In individuals who had ever used a BZRA medication, the relative risk was 2.03 times higher for prior BZRA users in comparison to those who had never used a BZRA and 1.49 times higher for prior BZRA users after adjusting for confounds. However, the authors were not clear about which confounding variables were controlled. In the analyses of recent BZRA usage and subsequent dementia, the risk for recent BZRA users was 1.93 times higher than never users and 1.55 times higher after adjusting for confounds. For those with past BZRA use and no recent use, the risk was 1.69 times higher than never users with the risk remaining 1.55 times higher after adjusting for confounds. There were only two studies in the analysis that reported dose-response findings, and the risk was found to be 1.22 times higher for those that took larger dosages of BZRAs. The primary limitations from this meta-analysis are the lack of adequate identification and control for confounding variables.

GREECE 2016

Most recently, Bellou et al. (2016) conducted a large review of systematic reviews and meta-analyses of environmental risk factors of dementia that included 27 meta-analyses. The authors determined that depression at any age, late-life depression, social isolation, and benzodiazepines were the variables that convey the most convincing risk. The authors did acknowledge that benzodiazepines may be prescribed for prodromal

symptoms of dementia which could confound the identification of the contribution of BZRAs to risk of dementia.

Relevant Case Controlled Studies

This section reviews the case controlled studies that evaluated the relationship between BZRA usage and subsequent dementia.

Quebec Insurance Claims

Billioti de Gage et al. (2014) utilized a case-controlled design within a national healthcare database in Quebec (n = 38,741) and identified individuals age 66 years old and older who had used a BZRA within 5-10 years prior to dementia diagnosis as their methodology to capture the prodromal phase. The authors did acknowledge that BZRA usage may be an indicator of an underlying condition, with symptoms of A/I as a risk factor for dementia. Increased cumulative prescribed dosages of benzodiazepines were associated with an increased risk for a subsequent Alzheimer's dementia billing diagnosis. The study did not include any clinical assessment.

Clinical Practice Research Datalink

Imfeld et al. (2015) conducted a case controlled analysis of dementia patients in the Clinical Practice Research Datalink (n = 26,459), a large healthcare database in the United Kingdom. The authors controlled for the prodromal phase of dementia by subtracting the time period from typical symptom onset to diagnosis; this was determined to be two years for Alzheimer's dementia and three years for vascular dementia. This study did control for several environmental confounds and comorbid conditions. After accounting for the prodromal phase, there was no association between benzodiazepine usage and risk for developing Alzheimer's dementia or vascular dementia. Additionally, the authors reported a lower risk of Alzheimer's dementia for long-term benzodiazepine users. This study

contradicts the proposal that BZRA usage causes dementia, because cumulative usage and longer-term use had a lower risk of subsequent dementia. The authors suggested that previous findings of increased dementia risk with BZRA usage was due to treatment during the dementia prodrome rather than a true causal link.

ADULT CHANGES IN THOUGHT STUDY

Recently, Gray et al. (2016) conducted a prospective case controlled analysis of individuals over the age of 65 that did not have dementia (n = 3,434) and evaluated subsequent dementia over an average of 7.3 years. The authors controlled for several medical and environmental comorbidities. To account for the prodromal phase, the authors identified the association at the time of diagnosis, at one year prior to diagnosis, and at two years prior to diagnosis. When looking at cumulative benzodiazepine dosage dispensed over 10 years and excluding the most recent year, larger cumulative benzodiazepine usage was associated with less risk for developing dementia. This study showed that the risk was highest for those at time of diagnosis, and the risk decreased at one year prior to diagnosis and was further decreased at two years prior to diagnosis. As with the Imfeld et al. study, this study clearly challenges the notion that BZRA usage causes dementia, again providing evidence that cumulative usage and longer-term use had a lower risk of subsequent dementia.

Other Medications and Dementia Risk

Studies have also found a relationship between other classes of medications and subsequent dementia, although the causal relationship is also undetermined. Gray et al. (2015) reported a relationship between anticholinergic medications—commonly used for treating insomnia—and subsequent dementia. Gomm, von Holt, Thomé, and et al. (2016) reported an association between proton pump inhibitors—commonly used to treat gastroesophageal reflux—and subsequent dementia. The fact that other medications have

been found to exhibit correlations with subsequent dementia suggests that the etiology of dementia may be frequently characterized by comorbid and precursor conditions that presage or, at least, precede dementia onset.

PRODROMAL DEMENTIA

Many individuals have multiple pathologies that underlie their dementia syndrome (Rizzi et al., 2014; WHO, 2016). The dementia phenotype will vary with the specific pattern of neurodegeneration (Nowrangi, 2015). The dementia prodrome is elusive, because the etiology is rarely clear, and there are methodological inconsistencies in clinical diagnoses and research study definitions (Rizzi et al., 2014).

Neuropsychiatric Indicators of Prodromal Dementia

Given that neuropsychiatric manifestations of developing dementia are likely present at least 2-5 years prior to the diagnosis of dementia (Belleville et al., 2014), and a dementia prodrome could cause elders to seek treatment for neuropsychiatric symptoms, such as anxiety and insomnia, a review of the evidence for the neuropsychiatric symptoms relevant to this study is presented.

ANXIETY

Recently, Petkus et al. (2016) conducted an analysis of the Swedish Adopted Twins Study of Aging that were assessed for anxiety in 1984 (n = 1082; mean age = 60.86) and were evaluated every three years until 2012. The authors found that anxiety scores at baseline were associated with an increased risk in dementia at the 28-year follow-up. The risk for subsequent dementia was higher for the dizygotic twin with higher anxiety at baseline. That risk difference was not significant for monozygotic twins indicates a genetic mediating factor. Additional analyses found that benzodiazepine usage at baseline did not influence the association between baseline anxiety scores and subsequent dementia.

In a recent meta-analysis, Gulpers et al. (2016) showed that anxiety increases the risk of CIND (cognitive impairment/not dementia) and dementia but is not a predictor of the conversion from CIND to dementia. Pietrzak et al. (2012) found that mild elevations in worry symptoms were associated with poorer performance on memory tasks and predicted subsequent cognitive decline; this finding was independent of depression or baseline cognitive functioning. Conversely, Ramakers et al. (2015) and de Bruijn et al. (2014) did not find anxiety to be related to subsequent dementia or cognitive impairment (DOCI).

INSOMNIA

Hahn et al. (2014) conducted a nine-year prospective study of Swedish elders (n = 214, average baseline age = 83.38). The risk of subsequent all-cause dementia was 75% higher for participants that reported a recent reduction in sleep duration; the risk was twice as high for Alzheimer's dementia. The risk of subsequent all-cause dementia was 2.5 times higher for participants that reported at least a moderate change in subjective sleeping pattern; the risk was three times as high for Alzheimer's dementia.

Elwood et al. (2011) identified a relationship between sleep disturbances and vascular dementia but not non-vascular dementia. Kabeshita et al. (2016) found that, for individuals in the early stage of Alzheimer's dementia, those with disturbed sleep were more likely to have a higher total NPI score—indicating a higher degree of neuropsychiatric symptom severity—and higher subscale scores for anxiety, euphoria, disinhibition, and deviant physical movement. REM sleep behavior disorder has been found to be a strong predictor of subsequent Parkinson's disease and Lewy body dementia (LBD) (Howell & Schenck, 2015; Iranzo et al., 2014). While the pathology of alpha-synucleinopathies (Parkinson's disease and LBD) differs from Alzheimer's dementia and vascular dementia, the fact that there is an identifiable prodromal symptom in another neurodegenerative disorder is supportive of the rationale to look for similar predictors in all dementias.

DEPRESSION

Several studies have identified a relationship between depression and subsequent dementia (Burke, Maramaldi, Cadet, & Kukull, 2016; Butters et al., 2008; Diniz, Butters, Albert, Dew, & Reynolds, 2013; Raji, Reyes-Ortiz, Kuo, Markides, & Ottenbacher, 2007). Mirza et al. (2016) found that only depression that is worsening was associated with subsequent dementia. A recent systematic review of meta-analyses by Bellou et al. (2016) concluded that depression in late-age is associated with subsequent dementia, and particularly for vascular dementia. Byers and Yaffe (2011) reviewed the evidence showing that early depression—before age 60—more consistently predicts subsequent dementia than late age depression. McCutcheon et al. (2016) found that a larger proportion of depressed Alzheimer's disease participants had neuritic plaques or neurofibrillary tangles, but the pathology was not related to depression severity. The mechanism likely responsible for the relationship between depression and subsequent DOCI is termed *the vascular depression hypothesis* (Bellou et al., 2016, p. 9; Byers & Yaffe, 2011, p. 5).

ANY NEUROPSYCHIATRIC SYMPTOM

Cooper et al. (2015) conducted a meta-analysis of the factors that predict the conversion from non-demented cognitive impairment (CIND) to dementia and found that the presence of at least one neuropsychiatric symptom in CIND predicts subsequent dementia. However, depression, anxiety, and neuropsychiatric symptom severity were not consistent predictors across the studies and were not significant predictors in the meta-analysis. This finding suggests that neuropsychiatric manifestations of the neurodegenerative process of dementia vary.

Biological Evidence of Prodromal Dementia

The section reviews the biological evidence for prodromal dementia.

BIOMARKERS

CSF biomarkers (Aβ42 and tau) have been associated with anxiety, agitation, irritability, sleep difficulty, and change in appetite in individuals with mild cognitive impairment (MCI) (Ramakers et al., 2013) and were shown to be altered 15-20 years before clinical Alzheimer's dementia manifests (Dubois et al., 2016). Multiple studies have identified an increased risk of subsequent dementia for neuropsychiatric symptoms in combination with the Alzheimer's disease risk gene APOEε4 (Beaudreau et al., 2013; Burke et al., 2016; Pink et al., 2015). Dubois et al. (2016) reported that amyloid and tau biomarkers may be used to diagnose preclinical dementia, although there are multiple measurement methods being studied.

NEUROIMAGING AND ELECTROPHYSIOLOGY

Moretti (2015) showed that EEG changes are able to identifying prodromal Alzheimer's dementia three years before diagnosis. Electrophysiology measurements have been shown to identify impaired visual short-term memory binding (associated with AD) and may be a useful tool for identifying early Alzheimer's dementia (Pietto et al., 2016). Cerebrovascular risk factors may affect integrity of white matter which may influence behavioral manifestations in Alzheimer's dementia (Wu et al.,2015). Depression in the early period of Alzheimer's dementia was not found to be related to neuritic plaques or neurofibrillary tangles (McCutcheon et al., 2016). This finding likely shows that the pattern of neurodegeneration predicts the symptom and not the pathology.

Late-life-onset-depression is associated with decreased brain volume and in certain brain structures (Andreescu et al., 2008). Low hippocampal volume has been associated with untreated depression, diabetes, and altered diastolic blood pressure (Elcombe et al., 2015) as well as apathy and anhedonia (Donovan et al., 2015). Subjective memory decline is associated with hippocampal atrophy (Cherbuin, Sargent-Cox, Easteal, Sachdev, &

Anstey, 2015). Individuals with MCI that have apathy have impaired metabolism in the posterior cingulate cortex (Delrieu et al., 2015).

Gaps in the Literature

While the association between BZRA treatment and subsequent dementia has been frequently described (Bellou et al., 2016; Billioti de Gage et al., 2015; Zhong et al., 2015), no studies have evaluated the potential role of late age onset A/I as a marker for developing dementia. The focus in this study was to identify whether A/I symptoms and non-BZRA treatments for A/I were also associated with subsequent dementia in order to determine whether the symptomatic presentation may be an indicator of developing dementia.

BZRA medications may contribute to the risk of subsequent dementia diagnosis, but these medications may also be targeting early symptoms in the dementia process. If the results of this study suggest that treatment with other medications for A/I also correlate with subsequent dementia, then the findings would support the idea that A/I are prodromal symptoms of dementia.

Summary

There is enough persistent evidence that neuropsychiatric symptoms, such as anxiety and insomnia, are implicated as precursor or prodromal indicators of subsequent cognitive impairment or dementia to justify more systematic study. There is a need to clarify the association between A/I symptoms and treatments and subsequent dementia in older adults. The conclusion that BZRA medications precipitate dementia cannot currently be made without knowing whether non-BZRA medications also appear to precipitate dementia. The first step toward this goal is to evaluate the association in those patients that have not used BZRAs to differentiate between the presence of a prodromal cluster or impact of medications. Determining whether other medications also predict subsequent

dementia is critical to evaluating whether particular medications precipitate dementia or if A/I is an early indicator of developing dementia necessitating treatment.

This study is significant as the first attempt to explore the A/I symptom cluster in prodromal dementia and to evaluate the association of dementia with non-BZRA treatments for A/I. Prescribers must possess the most evidence-based information to treat patients and be able to confidently explain the current warnings to patients. As a result of this study, researchers and clinicians in the field have new information regarding the associations found between some medications for A/I and subsequent dementia which places the previous findings in a larger meaningful context. Additionally, researchers have information that may guide future study. If future studies also find that non-BZRA medications are predictive of subsequent dementia, this may contribute to earlier identification and treatment.

The research conducted is innovative because it changes the discussion of dementia from causative factors to predictive factors. The previous literature supports the idea that new-onset A/I in older adults is a potential screening marker for developing dementia. In addition to identifying environmental factors that contribute to morbidity, this approach shifts the focus to early identification.

CHAPTER 3

Methodology

OBJECTIVE

The long-term goal is to understand the contributing factors to the development of dementia, with a focus on early identification and prevention. The overall objective of this study was to clarify whether A/I symptoms or treatment is associated with subsequent dementia diagnosis; this knowledge is crucial to achieve our long-term goal. The objective of this study was to explore the relationship between new-onset A/I symptoms and non-BZRA medication treatments and subsequent DOCI. This study looked specifically at the symptom cluster that is treated by BZRA medications and the other medication treatments for those symptoms. This study proposed to test the postulate that A/I is an independent predictor of dementia.

DESIGN

This study was a retrospective data analysis of the ADAMS dataset following the work of Billioti de Gage et al. (2014), Beaudreau et al. (2013), Amieva et al. (2008), Petkus et al. (2016) and the recommendations for future study by Billioti de Gage et al. (2015) and Salzman and Shader (2015).

Data Description

THE AGING, DEMOGRAPHICS, AND MEMORY STUDY

The Aging, Demographics, and Memory Study (ADAMS, 2007) study is a supplement to the Health and Retirement Study (HRS), which is sponsored by the National Institute of Aging (grant number NIA U01AG009740). The ADAMS was conducted jointly by Duke University and the University of Michigan in four sequential waves: Wave

A (August 2001 – December 2003), Wave B (November 2002 – March 2005), Wave C (June 2006 – May 2008), and Wave D (January 2008 – December 2009). Participants did not progress to the next wave once they received a dementia diagnosis. Attrition from the study also occurred due to death or unexplained reasons.

Wave B only evaluated individuals with compromised cognitive function in Wave A, whereas all available eligible participants were evaluated in Waves C and D. Wave B clarified the cognitive functioning for Wave A participants with subclinical cognitive dysfunction on the intake assessment. Neuropsychological assessments lasted three to four hours and included the participants, a family member or other informant, a nurse, and a specifically trained neuropsychology technician. In addition to the questionnaires and neuropsychological tests, the nurse collected vital signs and a tissue sample. Diagnoses in the ADAMS were agreed upon by a panel at Duke University that consisted of a geriatric psychiatrist, a neurologist, a neuropsychologist, and a cognitive neuroscientist (University of Michigan, 2013).

The ADAMS did included individuals with diagnoses of 'cognitive impairment but not demented' (CIND). In this study, we excluded individuals with evidence of cognitive dysfunction in Waves A or B.

The Neuropsychiatric Inventory

The Neuropsychiatric Inventory (NPI) was developed to assess neuropsychiatric symptoms in dementia (Cummings et al., 1994). The NPI assessed 10 domains in the ADAMS: delusions, hallucinations, agitation, depression, apathy, elation, anxiety, disinhibition, irritability, and aberrant motor behavior. In the down-selection phase, apathy and suicidal ideation variables for the depression construct were included, but later excluded due to inadequate frequencies. For this study, the new-onset or worsened symptom qualifier for anxiety, agitation, irritability, and depression was used to differentiate the prodromal process from any chronic pre-existing symptoms.

In the NPI survey for the ADAMS, three questions about sleep were added to the questionnaire: trouble sleeping, frequent awakenings, and early wakening. However, frequent awakenings and early wakening were excluded due to inadequate frequencies. Additionally, disruptions in sleep may be due to confounds such as nocturia that are not logically related to cognitive decline. The survey did not include a new onset or worsened symptom qualifier for the trouble sleeping variable.

Cummings et al. (1994) confirmed the content validity of the NPI by consulting with 10 international experts in geriatrics, neurology, and neuropsychology. The authors tested the concurrent validity by comparing the subscale scores of the NPI to the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), the Hamilton Rating Scale for Depression (HAM-D); all subscale measures were significantly correlated with the corresponding item on the BEHAVE-AD or HAM-D. Interrater reliability was between 93.6 and 100% on all subscale measures, and the test-retest reliability coefficient was .79 overall and .86 for symptom severity. From the analysis of homogeneity, the Cronbach's alpha was .88 overall with minimal item variation. Inter-item correlations were significant in 22% of the items on the NPI—for instance, items from depression were correlated with items from anxiety and apathy. The study by Cummings et al. included 45 participants with dementia—42 had Alzheimer's dementia, one had vascular dementia, and two had unspecified dementia—and 20 controls; the study sample included 26 males and 19 females, and the controls were evenly divided by gender. The mean age of the total sample 75.5. Unfortunately, no data was available regarding the reliability data for the NPI in the ADAMS. All studies identified referenced the Cummings et al. data.

Sampling and Sample Description

The down-selection process started with a random sample of 1770 participants over the age of 70 selected from the HRS for the ADAMS (University of Michigan, 2013) in a preliminary assessment. Of this random sample, a total of 856 participants meeting study

criteria completed the first wave of assessments (227 participants died before their assessment and 687 either refused or could not be located) (Table 3.1). The ADAMS evaluated participants in Waves C that were not found to have dementia in Waves A or B further reducing the sample to 315.

Inclusion Criteria

The primary inclusion criteria for this study was participation in the ADAMS and completion of survey data for Wave A and Wave C.

Exclusion Criteria

BZRA usage at any wave of the ADAMS was excluded (n = 45) to eliminate any potential interference with the interpretation of non-BZRA usage. We excluded 172 participants with comorbid medical conditions that represent confounding factors to assessment or etiological interpretation. DOCI x gender breakdown did not demonstrate differential rates in the excluded sample (Table 3.2).

The exclusion criteria (Table 3.3) consist of confounding variables that explain alternative potential causes of cognitive decline or interfere with cognitive or neuropsychiatric assessment. Neurological conditions interfere with the measurement of cognition and the interpretation of the etiology of altered cognitive findings. Sleep apnea confounds the interpretation of the insomnia variable. Current alcohol problem confounds the interpretation of cognitive assessment. Cardiovascular disease and congestive heart failure are known risk factors for vascular and non-vascular dementia (Cermakova et al., 2015).

The final study sample included 143 participants (Table 3.4). In the study sample, gender was not associated with subsequent DOCI ($\chi^2(1) = 0.30$, $p = .58$); however within gender analyses did uncover differential incidence rates in exposed and non-exposed

patients (discussed below). No other demographic variables were controlled. The ADAMS is a cohort study with similar ages for both genders.

Table 3.1 Study Sample

Sample	Removed	n
HRS Sample		1770
Deceased before Wave A	227	
Did not participate[1]	687	
Wave A Sample		856
Wave B Sample[2]		252
Dementia in Wave A or B	348	
Deceased or other before Wave C	193	
Wave C Sample		315
Wave D Sample[3]		217
Exclusion Sample	172	
Total Study Sample[4]		143

Note. 1—Either refused or unable to locate. 2—Not all Wave C participants were evaluated in Wave B, because Wave B was subsample that was selected to clarify Wave A cognitive function. 3—We did not include Wave D participants unavailable in Wave C. 4—The study sample equals all participants assessed in Wave C that did not meet an exclusion criteria.

Table 3.2 Exclusion Sample Description

Gender	Total #	DOCI #	DOCI %
Male	93	42	45
Female	79	34	43
Total	172	76	44

Table 3.3 Exclusion Criteria Frequencies

Variable	n
BZRA usage[1]	45
DOCI in Wave A OR B	16
Neurological diagnosis[1]	52
Cardiovascular history[1]	67
Brain trauma history[1]	36
Prior neurocognitive diagnosis[1,2]	3
History of treatment for seizures[1]	8
History of sleep apnea[1]	8
Current problem with alcohol[1]	12

Note. 1—Wave A to D. 2—Prior neurocognitive history includes participants that reported prior diagnosis for dementia, stroke, transient ischemic attack, or Parkinson's disease after evaluation due to memory concerns.

Table 3.4 Sample Description

Gender	n	DOCI	DOCI %	Mean Age at Intake (SD)	Mean Age at Intake if Later DOCI (SD)	Mean Age at DOCI Diagnosis (SD)
Male	62	18	29.0	77.55 (5.41)	78.56 (6.04)	83.28 (5.79)
Female	81	27	33.3	77.42 (5.03)	78.15 (5.27)	83.63 (5.36)
Total	143	45	31.5	77.48 (5.18)	78.31 (5.53)	83.49 (5.47)

Data Analysis

Data was analyzed using SPSS (Version 24) and MedCalc (Version 17.0.4). Significance was calculated at $\alpha = .05$. The sample size was determined by the ADAMS dataset and the inclusion and exclusion criteria. An a priori power analysis was not conducted, as the sample size was fixed based on the a priori selection process.

SPSS (Version 24) was used to calculate chi-square test of association (χ^2), Fisher's exact test (used when the expected frequency is less than 5), and for logistic regression analysis—including sensitivity and specificity. Sensitivity reflects the degree to which the assessment would identify individuals with any possibility of having the condition—i.e., dementia. High sensitivity would run the risk of many false positives—including many who actually do not have the condition. Specificity reflects the accuracy of the assessment; high specificity results in false negatives—incorrectly excluding those that have the condition. Both of these values provide additional information about the utility of the measures being used to predict dementia.

MedCalc (Version 17.0.4) was used to calculate the relative risk (RR), odds ratios (OR), and to compare incidence rates (IR). The RR and OR are related calculations that attempt to answer similar questions (Portney & Watkins, 2009). The RR is the ratio of a dichotomous outcome for a given exposure to the alternative outcome if not exposed. The OR is the ratio of the odds of a dichotomous outcome for a given exposure to the odds of the same outcome if not exposed.

Incidence rate is a measure of frequency over a given interval time period—i.e. number of months or years (Portney & Watkins, 2009). The variable *number-month* represents the number of months from the first assessment to the last assessment—either Wave C or D, depending on dementia diagnosis or drop out before Wave D. Incidence rate calculation in this study was the frequency count for DOCI divided by the number-month. For this calculation, participants were separated by the Wave A symptom variable, and the frequency count for DOCI in Wave C or D for each was divided by number-months in order to determine the incident rate for each group. Appendix A displays the frequencies of these calculations. MedCalc (Version 17.0.4) was used to compare the incidence rates of the two groups to compare the difference between incidence rates, the incidence rate ratios, and the level of significance.

SPECIFIC AIM 1

Evaluate the association between A/I symptoms and subsequent DOCI among participants in the Aging, Demographics, and Memory Study (ADAMS).

Research Question 1.1 Do cognitively normal individuals with A/I symptoms in Wave A have an increased incidence of DOCI in Waves C or D in comparison to those that did not have A/I symptoms in Wave A?

Analysis: Compare the incidence rates of DOCI in Waves C or D for two groups (with/without A/I symptoms in Wave A).

Research Question 1.2 Do cognitively normal individuals with anxiety, insomnia, and depressive (A/I/D) symptoms in Wave A have an increased incidence of DOCI in Waves C or D in comparison to those that did not have A/I/D symptoms in Wave A?

Analysis: Compare the incidence rates of DOCI for two groups (with/without A/I/D symptoms Wave A).

SPECIFIC AIM 2

Evaluate the association between non-BZRA anxiolytic medications or sleep aids (A/I medications) and subsequent DOCI among participants in the ADAMS.

Research Question 2.1 Do cognitively normal individuals that reported using A/I medications in Wave A have an increased incidence of DOCI in Waves C or D in comparison to those that did not report using A/I medications in Wave A?

Analysis: Compare the incidence rates of DOCI for two groups (with/without A/I medications Wave A).

SPECIFIC AIM 3

Evaluate the association between anxiety, depressive, and insomnia symptoms, the usage of A/I medications, and subsequent DOCI among participants of the ADAMS.

Research Question 3.1 What is the best set of predictors (A/I medication usage, A/I/D symptoms, gender) from Wave A of developing DOCI in Wave C or D?

Analysis: Conduct full model and stepwise logistic regression analyses to assess the unique and combined risks for DOCI.

Study Variables

Independent variables were created by compiling composite grouping variables based on the presence or absence of selected prodromal conditions (new-onset or worsened anxiety, sleep, or depression indicators) and rolled up into larger indices reflecting the presence of any of a set or a summative variable reflecting the combined contribution of a set. These combinatory sets are outlined below.

DEPENDENT VARIABLE

Dementia Variable (Wave C or D)

- DOCI (Dementia or cognitive impairment)—[Dichotomous]

INDEPENDENT VARIABLES

Anxiety Variables (Wave A) ➔

- Anxiety—New onset or worsened anxiety—[Dichotomous]
- Agitation—New onset or worsened agitation—[Dichotomous] ➔
- Irritability—New onset or worsened irritability—[Dichotomous]

    - **AnyAnx**—Any anxiety, agitation, or irritability symptom—[Dichotomous]

Anxiety for individuals with dementia is difficult to define due to symptom overlap and varied definitions of terms such as anxiety, agitation, and irritability (Seignourel, Kunik, Snow, Wilson, & Stanley, 2008).

Sleep Variables (Wave A) ➔

- **Insomnia**—[Dichotomous]

The variables for frequent wakening and early wakening were initially considered but were not included in the analysis. The sample frequencies were too low, and the causes of these symptoms are likely related to comorbid variables such as enuresis and environmental factors that are not reasonably related to a neurodegenerative.

Depression Variables (Wave A) ➔

- **Depression**—New-onset or worsened depression—[Dichotomous]

The frequencies for suicidal ideation and apathy were originally planned for the analysis, but the frequencies were inadequate and were not used.

A/I Medication Variables (Wave A) ➔

- **A/I Med Use**—Any anxiety ***OR*** insomnia medication reported in Wave A—[Dichotomous] ➔
    - **A/I Medication Count**—Sum of A/I medications reported in Wave A—[Interval]

Medication names are coded in the ADAMS with Druglook, a coding system developed at Duke University (University of Michigan, 2013). The medication data was collected on the surveys completed at Waves A to D and represented the medications the participant reported taking during the previous two-week period. Additional variables, such as dosage and number of pills taken, were not used due to incompleteness.

Lists of medications (Appendix B) that are used to treat anxiety and insomnia were generated from Stahl (2014). A separate list was created for BZRA medications. The anxiety and insomnia medication lists were combined, and the BZRA medications were removed from the combined list. Note that almost all antidepressant medications are used to treat anxiety, and many anxiety medications are also indicated for insomnia. Appendix B displays the medication lists.

Combined Index Variables (Wave A) ➔

A/I—AnyAnx ***OR*** insomnia—[Dichotomous]

AnyAnx and Insomnia—AnyAnx ***AND*** insomnia—[Dichotomous]

Sum of A/I Symptoms—Anxiety, agitation, irritability, ***OR*** insomnia—[Interval]

AnyAnx and Depression. And Insomnia—[Dichotomous]

A/I+D—(A/I) ***AND*** depression—[Dichotomous]

A/I-D—(A/I) ***AND*** not depressed—[Dichotomous]

Additional Variables

Gender—[Dichotomous]

HUMAN SUBJECTS

This study used publicly available, existing, de-identified data, and the University of Texas Medical Branch Institutional Review Board (IRB) approved the study under exempt status. This study did not involve interaction with any human subjects.

CONFIDENTIALITY AND DATA SECURITY

The ADAMS dataset is deidentified, and all data analysis was conducted on a single personal computer. Syntax files were used for data preparation. The use of syntax facilitates an audit trail. Every step of the analysis can be retraced, and all variable transformations and data analyses can be efficiently repeated if there is any question or uncertainty.

CHAPTER 4

Results

SPECIFIC AIM 1

Evaluate the association between A/I symptoms and subsequent DOCI among participants in the Aging, Demographics, and Memory Study (ADAMS).

Research Question 1.1

Research Question 1.1 asked whether cognitively normal individuals with A/I symptoms in Wave A have an increased incidence of DOCI in Waves C or D in comparison to those that did not have A/I symptoms in Wave A?

The cross-tabulation analyses for independent variables by DOCI (Table 4.1) showed that there was only one female that had both an anxiety symptom (anxiety, agitation, or irritability) and insomnia, and there were zero males. This finding is likely the result of the small sample size. For this reason, the most inclusive compilation was to include those with *either* any anxiety symptom (anxiety, agitation, or irritability) or insomnia (A/I).

Chi Square/Fisher's Exact tests of association (Table 4.2) found no significant association between any combination of A/I symptoms in Wave A and DOCI in Waves C or D for the total group ($p = .40$). However, a closer examination within gender revealed a marginally significant association between agitation and DOCI for males ($p = .08$). The association was further strengthened when insomnia ($p = .03$) was included in the Wave A variable set (this added one additional patient). While the statistical comparisons in incidence (Table 4.3) between A/I symptoms in Wave A and DOCI in Waves C or D suggested a significant difference for males ($p = .04$) who demonstrated A/I symptoms in Wave A, the finding is not deemed significant, because the confidence interval includes

the value 1. As with the Fisher's Exact tests, the comparison of incidence was not significant for females (p = .45) or the total group (p = .43).

Relative risk and odds ratio analyses (Table 4.4) clearly show the higher risk for males of developing DOCI is 2.65 times (p = .01) and the odds of developing DOCI is almost 5 times as great for males in Wave D if demonstrating A/I symptoms in Wave A compared to those who do not (p = .02). These findings suggest that the neuropsychiatric manifestations of prodromal dementia differ for males and females.

Table 4.1 Cross Tabulation for Symptom Variables by DOCI and Gender

	DOCI in C or D											
	MALE				FEMALE				TOTAL			
	No		Yes		No		Yes		No		Yes	
Wave A Variables	#	%	#	%	#	%	#	%	#	%	#	%
Anxiety[1]												
No	44	71	17	27.4	51	63	27	33.3	95	66.4	44	30.8
Yes	0	0	1	1.6	3	3.7	0	0	3	2.1	1	0.7
Agitation[1]												
No	44	71	16	25.8	53	65.4	27	33.3	97	67.8	43	30.1
Yes	0	0	2	3.2	1	1.2	0	0	1	0.7	2	1.4
Irritability[1]												
No	44	71	18	29	53	65.4	25	30.9	97	67.8	43	30.1
Yes	0	0	0	0	1	1.2	2	2.5	1	0.7	2	1.4
AnyAnx[1,2]												
No	44	71	16	25.8	50	61.7	25	30.9	94	65.7	41	28.7
Yes	0	0	2	3.2	4	4.9	2	2.5	4	2.8	4	2.8
Insomnia[3]												
No	39	62.9	13	21	46	56.8	25	30.9	85	59.4	38	26.6
Yes	5	8.1	5	8.1	8	9.9	2	2.5	13	9.1	7	4.9
AnyAnx and Insomnia[4]												
No	44	71	18	29	53	65.4	26	32.1	97	67.8	44	30.8
Yes	0	0	0	0	1	1.2	1	1.2	1	0.7	1	0.7
A/I[5]												
No	39	62.9	11	17.7	43	53.1	24	29.6	82	57.3	35	24.5
Yes	5	8.1	7	11.3	11	13.6	3	3.7	16	11.2	10	7

Note. 1 - New or worsened symptoms. 2 - *AnyAnx* includes anxiety, agitation, or irritability. 3 - *Insomnia* indicates trouble falling asleep (not a new or worsened condition). 4 - Inadequate observed values for analysis. 5 - A/I (Any anxiety symptom or insomnia) is the primary target variable.

Table 4.2 Chi-Square and Fisher's Exact Tests for Independent Variables by DOCI And Gender

		Anxiety			Agitation			Irritability$_1$		
		Pearson χ^2		Fisher's Exact	Pearson χ^2		Fisher's Exact	Pearson χ^2		Fisher's Exact
Gender	n	χ^2	p	p	χ^2	p	p	χ^2	p	p
Males	62	-	-	.29	-	-	.08*	-	-	-
Females	81	-	-	.55	-	-	1.00	-	-	.26
Total	143	-	-	1.00	-	-	.23	-	-	.23
		Any Anxiety			Insomnia			Any Anxiety or Insomnia (A/I)		
Males	62	-	-	.08*	-	-	.14	-	-	.03**
Females	81	-	-	1.00	-	-	.48	-	-	.37
Total	143	-	-	.26	0.13	.71	-	0.72	.40	-

Note. Omitted values indicate whether chi-square assumption is violated. If expected frequency < 5, Fisher's test is used. Pearson χ^2 significance level is asymptotic and 2-sided. Fisher's Exact Test for significance is 2-sided. Most inclusive group used for subsequent comparative analyses.
1—Irritability values not calculated for males due to zero frequency.
* p < .10. ** p < .05.

Table 4.3 Comparison of Incidence Rates for A/I by DOCI and Gender

Measure	Males	Females	Total
Group 1 IR	.0034	.0054	.0046
95% CI	[.0017, .0062]	[.0034, .0080]	[.0032, .0063]
Group 2 IR	.0091	.0034	.0060
95% CI	[.0037, .0187]	[.0007, .0099]	[.0029, .0111]
IR difference	-.0056	.0020	-.0015
95% CI	[-.0110, -.0003]	[-.0031, .0071]	[-.0052, .0022]
p	.04**$_1$	.45	.43
IRR	0.38	1.5800	0.75
95% CI	[.13, 1.15]$_1$	[.48, 8.19]	[.37, 1.71]

Note. IR = incidence rate; CI = confidence interval; IRR = incidence rate ratio.
1—Confidence interval includes the value 1; non-significant finding.
** p < .05.

Table 4.4 Relative Risk and Odds Ratio for A/I by DOCI and Gender

Measure	Males	Females	Total
Relative Risk	2.65	0.60	1.29
95% CI	[1.3064, 5.3816]	[0.2087, 1.7147]	[0.7346, 2.2503]
z statistic	2.7	0.956	0.88
p	.01**	.34	.38
Odds Ratio	4.96	0.49	1.46
95% CI	[1.3148, 18.7392]	[0.1241, 1.9246]	[0.6051, 3.5432]
z statistic	2.36	1.02	.85
p	.02**	.31	.40

Note. ** p < .05.

Research Question 1.2

Research Question 1.2 asked if cognitively normal individuals with anxiety, insomnia, and depressive (A/I/D) symptoms in Wave A have an increased incidence of DOCI in Waves C or D in comparison to those that did not have A/I/D symptoms in Wave A?

Cross-tabulation analyses (Table 4.5) indicated that comparison groups composed of those with all three conditions (any anxiety, insomnia, and depression) were virtually non-existent. This finding is again likely due to small sample size. Although there were six participants with both A/I and depression, only one of those individuals reported having both an anxiety symptom and insomnia. Therefore, the most inclusive compilation was to include patients who had depression *and* also at least one A/I symptom (anxiety, agitation, irritability, or insomnia).

Chi Square/Fisher's Exact tests of association (Table 4.6) found no significant association between Wave A depression ($p = .46$), A/I-D ($p = .71$), or A/I+D ($p = .38$) and subsequent DOCI for the total group. A closer examination within gender revealed a marginally significant association between A/I+D and subsequent DOCI for males ($p = .08$). In comparison to the analysis of any anxiety symptom, these findings are identical for males. In this sample, the two depressed males with subsequent DOCI also had at least one anxiety symptom (anxiety, agitation, or irritability).

Statistical comparisons in incidence rates (Table 4.7 and Table 4.8) suggested that males with both A/I and depression were more likely to develop DOCI ($p = .03$); however, since the confidence interval includes the value 1, this finding must be taken with considerable caution and is most likely due to the small sample size and heterogeneity in the sample. Likewise, marginal significance was found for non-depressed males with A/I, but the confidence interval invalidates this finding. There were no significant findings for

females or total group without controlling for gender in either the with or without depression variables.

Evaluation of relative risk and odds ratios (Table 4.9 and Table 4.10) identified a similar pattern. The risk of developing DOCI is 3.75 times greater ($p < .01$, [2.46, 5.71]) for males with both A/I and depression. The odds ratio calculation resulted an extremely large confidence interval due to the small sample size and should not be interpreted. There were no significant findings for females. These findings reinforce the presence of gender differences in the neuropsychiatric symptoms of prodromal dementia.

Table 4.5 Cross Tabulation for Anxiety and/or Insomnia and Depression (A/I/D) by DOCI and Gender

	DOCI in C or D											
	MALE				FEMALE				TOTAL			
	No		Yes		No		Yes		No		Yes	
Wave A Variables	#	%	#	%	#	%	#	%	#	%	#	%
Depression												
No	42	67.7	16	25.8	51	63	25	30.9	93	65	41	28.7
Yes	2	3.2	2	3.2	3	3.7	2	2.5	5	3.5	4	2.8
AnyAnx and depression and insomnia[1,2]												
No	44	71	18	29	54	66.7	26	32.1	98	68.5	44	30.8
Yes	0	0	0	0	0	0	1	1.2	0	0	1	0.7
A/I and not depressed (A/I-D)[3]												
No	39	62.9	13	21	46	56.8	25	30.9	85	59.4	38	26.6
Yes	5	8.1	5	8.1	8	9.9	2	2.5	13	9.1	7	4.9
A/I and depressed (A/I+D)[4]												
No	44	30.8	16	11.2	51	35.7	26	18.2	95	66.4	42	29.4
Yes	0	0	2	1.4	3	2.1	1	0.7	3	2.1	3	2.1

Note. 1 - Includes only those with all of AnyAnx (anxiety, agitation, or irritability) and depression and insomnia. 2 - Inadequate frequencies for analysis. 3 – Includes individuals with A/I that are not depressed. 4 - Includes only those with A/I that are also depressed.

Table 4.6 Chi-Square and Fisher's Exact Tests With/Without Depression by DOCI and Gender

		Depression			A/I and Not Depressed (A/I-D)			A/I and Depressed (A/I+D)		
		Pearson χ^2		Fisher's Exact	Pearson χ^2		Fisher's Exact	Pearson χ^2		Fisher's Exact
Gender	n	χ^2	p	p	χ^2	p	p	χ^2	p	p
Males	62	-	-	.57	-	-	.14	-	-	.08*
Females	81	-	-	1.00	-	-	.48	-	-	1.00
Total	143	-	-	.46	0.13	.71	-	-	-	.38

Note. Omitted values indicate whether chi-square assumption is violated. If expected frequency < 5, Fisher's test is used. Pearson χ^2 significance level is asymptotic and 2-sided. Fisher's Exact Test for significance is 2-sided.
* p < .10.

Table 4.7 Comparison of DOCI Incidence Rates (A/I-D)

Measure	Males	Females	Total
Group 1 IR	.0039	.0053	.0047
95% CI	[.0021, .0067]	[.0034, .0078]	[.0033, .0065]
Group 2 IR	.0076	.0032	.0054
95% CI	[.0025, .0177]	[.0004, .0116]	[.0022, .0112]
IR difference	-.0036	.0021	-.0007
95% CI	[-.0093, .0020]	[-.0038, .0080]	[-.0048, .0034]
p	.20	.49	.73
IRR	0.52	1.65	0.87
95% CI	[0.17, 1.86]	[0.41, 14.35]	[0.38, 2.30]

Note. IR = incidence rate; CI = confidence interval; IRR = incidence rate ratio; A/I-D = A/I and Not Depressed.

Table 4.8 Comparison of DOCI Incidence Rates (A/I+D)

Measure	Males	Females	Total
Group 1 IR	.0042	.0051	.0047
95% CI	[.0024, .0067]	[.0033, .0075]	[.0034, .0063]
Group 2 IR	0.0182	0.0038	0.0081
95% CI	[.0022, .0657]	[.0001, .0214]	[.0017, .0237]
IR difference	-0.014	0.0012	-0.0034
95% CI	[-.0268, -.0013]	[-.0076, .0101]	[-.0106, .0038]
p	.03**$_1$	0.78	0.35
IRR	0.23	1.32	0.58
95% CI	[0.05, 2.05]$_1$	[0.22, 54.26]	[0.18, 2.91]

Note. IR = incidence rate; CI = confidence interval; IRR = incidence rate ratio; A/I+D = A/I and Depressed.
1—Confidence interval includes the value 1; non-significant finding.
** p < .05.

Table 4.9 Relative Risk and Odds Ratio (A/I and Not Depressed)

Measure	Males	Females	Total
Relative Risk	2.00[1]	0.57	1.13
95% CI	[0.92, 4.36][1]	[0.16, 2.04]	[0.59, 2.18]
z statistic	1.75	0.87	0.37
p	.08*[1]	.39	.71
Odds Ratio	3.00	0.46	1.20
95% CI	[0.75, 12.04]	[0.09, 2.33]	[0.45, 3.26]
z statistic	1.55	0.94	0.37
p	.12	.35	.71

Note. 1—Confidence interval includes the value 1; non-significant finding.
* p < .10.

Table 4.10 Relative Risk and Odds Ratio (A/I and Depressed)

Measure	Males	Females	Total
Relative Risk	3.75	0.74	1.63
95% CI	[2.46, 5.71]	[0.13, 4.16]	[0.70, 3.77]
z statistic	6.17	0.34	1.14
p	< .01***	.73	.25
Odds Ratio	13.48[1]	0.65	2.26
95% CI	[0.61, 295.92][1]	[0.06, 6.60]	[0.44, 11.67]
z statistic	-	0.36	.98
p	.10[1]	.72	.33

Note. 1—Confidence interval includes the value 1; non-significant finding.
*** p < .01.

SPECIFIC AIM 2

Evaluate the association between non-BZRA anxiolytic medications or sleep aids (A/I medications) and subsequent DOCI among participants in the ADAMS.

Research Question 2.1

Research Question 2.1 asked whether cognitively normal individuals that reported using A/I medications in Wave A have an increased incidence of DOCI in Waves C or D in comparison to those that did not report using A/I medications in Wave A?

Cross-tabulation analyses (Table 4.11) shows that females in this sample used more A/I medications than males in this sample. Chi Square/Fisher's Exact tests of association (Table 4.12) found no significant association between A/I medication usage in

Wave A and incidence of DOCI in Waves C or D (p = .78). Gender did not influence this finding. Statistical comparisons in incidence rates (Table 4.13), relative risk (Table 4d), and odds ratio (Table 4.14) did not identify any association between A/I medication usage and subsequent DOCI with or without controlling for gender.

Additional analysis—without removing exclusion variables—did confirm a significant association between A/I medication usage and BZRA usage ($\chi^2(1) = 11.93$, n = 315, p = .001), which indicates that both medication groups—BZRA medications and non-BZRA A/I medications—were used by participants to treat the same target symptoms. This finding supports the idea that A/I medication usage may be a proxy to identify the same target symptoms that BZRA medications treat. Further analysis found that BZRA usage was not associated with subsequent DOCI ($\chi^2(1) = 0.57$, p = .45); this finding is counter to studies that have demonstrated a positive association between BZRA usage and subsequent dementia.

Table 4.11 Cross Tabulation for A/I Medication Usage by DOCI and Gender

	DOCI in C or D											
	Male				Female				Total			
	No		Yes		No		Yes		No		Yes	
Wave A Var.	#	%	#	%	#	%	#	%	#	%	#	%
A/I Med Use[1]												
No	40	64.5	17	27.4	46	56.8	23	28.4	86	60.1	40	28.0
Yes	4	6.5	1	1.6	8	9.9	4	4.9	12	8.4	5	3.5

Note. 1 - Usage of any anxiety or insomnia medications in Wave A.

Table 4.12 Chi-Square and Fisher's Exact Tests for A/I Medication Usage by DOCI and Gender

		A/I Medication Usage		
		Pearson χ^2		Fisher's Exact
Gender	n	χ^2	p	p
Males	62	-	-	1.00
Females	81	-	-	1.00
Total	143	0.04	.85	-

Note. Omitted values indicate whether chi-square assumption is violated. If expected frequency < 5, Fisher's test is used. Pearson χ^2 significance level is asymptotic and 2-sided. Fisher's Exact Test for significance is 2-sided.

Table 4.13 Comparison of Incidence Rates for A/I Medication Usage by DOCI and Gender

Measure	Males	Females	Total
Group 1 IR	.0047	.0051	.0049
95% CI	[.0027, .0075]	[.0032, .0076]	[.0035, .0067]
Group 2 IR	.0028	.0049	.0043
95% CI	[.0001, .0158]	[.0013, .0126]	[.0014, .0100]
IR difference	.0019	.0001	.0006
95% CI	[-.0055, .0092]	[-.0052, .0054]	[-.0037, .0049]
p	.62	.96	.78
IRR	1.66	1.03	1.14
95% CI	[0.26, 69.22]	[0.35, 4.09]	[0.45, 3.71]

Note. IR = incidence rate; CI = confidence interval; IRR = incidence rate ratio.

Table 4.14 Relative Risk and Odds Ratio for A/I Medication Usage by DOCI and Gender

Measure	Males	Females	Total
Relative Risk	0.93	0.67	1.00
95% CI	[0.42, 2.02]	[0.11, 4.04]	[0.42, 2.38]
z statistic	0.19	0.44	0.00
p	.85	.66	1.00
Odds Ratio	0.90	0.59	1.00
95% CI	[0.30, 2.71]	[0.06, 5.66]	[0.27, 3.67]
z statistic	0.19	0.46	0.00
p	.85	.65	1.00

SPECIFIC AIM 3

Evaluate the association between anxiety, depressive, and insomnia symptoms, the usage of A/I medications, and subsequent DOCI among participants of the ADAMS.

Research Question 3.1

Research Question 3.1 asked which set of independent variables from Wave A (A/I medication usage, A/I/D symptoms, gender) best predicts DOCI in Wave C or D? To answer this question, a series of logistic regression analyses were conducted to evaluate the effects of anxiety, depression, insomnia, and A/I medication usage in Wave A on the likelihood of DOCI in Wave C or D.

LOGISTIC REGRESSION, TOTAL SAMPLE

Preliminary analyses indicated a high degree of collinearity between the binary individual neuropsychiatric symptom variables as well as with A/I medication usage. Therefore, the logistic regression analysis was completed with dichotomous predictors and with summative index variables. A summative interval level index variable was created (0-4) which represented a count of any A/I symptom (anxiety, agitation, irritability, or insomnia). A summative variable reflecting the number of A/I medications was used in place of the dichotomous A/I medication usage variable. New-onset or worsened depression was retained as a dichotomous categorical variable (present/absent).

Model 1, Dichotomous Predictors

Full model logistic regression analysis was conducted to evaluate the effect of anxiety, agitation, irritability, depression, insomnia, A/I medication usage, and gender in Wave A on the likelihood of DOCI in Wave C or D.

The omnibus full model with all variables included was not significant ($\chi^2(7) = 3.46$, $p = .84$) with no predictor variables in the model demonstrating individual significance in predicting DOCI (Table 4.15). The variation in the dependent variable explained by the model was 3.4% (Nagelkerke R^2). The full model correctly classified subsequent DOCI 69.2% of the time (Table 4.16) with sensitivity (ability to classify true positives) very low (4.4%) and specificity (ability to classify true negatives) very high (99.0%). The false positive rate is 1.0% and positive predictive value is 66.7%. The false negative rate is 95.6% and negative predictive value is 69.3%.

Table 4.15 Model 1 Dichotomous Predictors Total Sample—Variables in the Equation

Predictors	B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
A/I Medication Usage	0.17	0.59	.77	1.18	0.38	3.73
Agitation	-1.50	1.65	.36	0.22	0.01	5.66
Anxiety	0.96	1.44	.50	2.61	0.16	43.47
Depression	-0.25	1.06	.82	0.78	0.10	6.18
Gender	-0.24	0.38	.52	0.79	0.37	1.66
Insomnia	-0.25	0.53	.63	0.78	0.28	2.18
Irritability	-0.85	1.45	.56	0.43	0.03	7.34

Note. Logistic regression model with all dichotomous predictor variables. Gender entered as dichotomous predictor.

Table 4.16 Model 1 Dichotomous Predictors Total Sample—Classification Table

		DOCI in C or D (Predicted)		
		No	Yes	% Correct
DOCI in C or D	No	97	1	99.0
(Observed)	Yes	43	2	4.4
Overall % Correct				69.2

Model 2, Summative Predictors

The logistic regression analysis was also conducted to evaluate the effect of the A/I symptom sum (interval), A/I medication count (interval), depression (dichotomous), and gender in Wave A on the likelihood of DOCI in Wave C or D.

With all variables included, the model was not significant, $\chi^2(4) = 1.44$, $p = .84$, with no individual variable reaching significance (Table 4.17). The variation in the dependent variable explained by the model was 1.4% (Nagelkerke R^2). The full model correctly classified subsequent DOCI 69.2% of the time (Table 4.18), and sensitivity (ability to classify true positives) was very low (2.2%). The specificity (ability to classify true negatives) was 100%; however, because the model only predicted DOCI in one participant, the false negative rate is 97.8% and negative predictive value is 69.0%.

Table 4.17 Model 2 Summative Predictors Total Sample—Variables in the Equation

Predictors	B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
A/I Medication Count	0.41	0.51	.43	1.50	0.55	4.11
Depression	-0.94	1.13	.41	0.39	0.04	3.60
Gender	0.27	0.44	.38	1.00	0.54	1.31
Sum of A/I Symptoms	-0.77	0.72	.29	0.47	0.12	1.89

Note. Logistic regression with summative predictor variables for A/I symptoms and A/I medication usage; depression and gender are dichotomous. Gender entered as dichotomous predictor.

Table 4.18 Model 2 Summative Predictors Total Sample—Classification Table

		DOCI in C or D (Predicted)		
		No	Yes	% Correct
DOCI in C or D	No	98	0	100.0
(Observed)	Yes	44	1	2.2
Overall % Correct				69.2

LOGISTIC REGRESSION, GENDER DIFFERENCES

Due to the evidence in Specific Aims 1 and 2 reflecting a differential pattern of incidence between the genders, it was desirable to assess predictive sets within each gender. Attempts to analyze dichotomous predictors within each gender failed; the persistence of multicollinearity and further lowered frequencies resulted in instability and violations of assumptions in the logistic regression computations. For these reasons, the within gender analyses were conducted using the summative predictors. Although analyses should be conservatively interpreted due to small sample sizes, the results are supportive of early trends.

Model 3, Summative Predictors, Male Gender

A logistic regression analysis was conducted within males to evaluate the effect of the A/I symptom sum (interval), A/I medication count (interval), and depression (dichotomous) in Wave A on the likelihood of DOCI in Wave C or D.

The model was marginally significant, $\chi^2(3) = 6.26$, p = .10. The variation in the dependent variable explained by the model was 13.7% (Nagelkerke R^2). Within the model (Table 4.19), the interval A/I symptom cluster variable is statistically significant for males, p = .03, and the odds of subsequent DOCI are 4.68 times greater for individuals with new-onset or worsened A/I symptoms in Wave A. However, A/I medication usage and new-onset or worsened depression were non-significant.

The within males model correctly categorized subsequent DOCI 75.8% of the time (Table 4.20); sensitivity (ability to classify true positives) is 38.9%; and specificity (ability to classify true negatives) is 90.9%. The false positive rate is 9.1% and positive predictive value is 63.6%. The false negative rate is 61.1% and negative predictive value is 78.4%.

Table 4.19 Model 3 Summative Predictors Male Gender—Variables in the Equation

					95% C.I.for EXP(B)	
Predictors	B	S.E.	Sig.	Exp(B)	Lower	Upper
A/I Medication Count	-0.68	1.22	.58	0.51	0.05	5.49
Depression	-0.63	1.19	.59	0.53	0.05	5.45
Sum of A/I Symptoms	1.54	0.69	.03**	4.68	1.20	18.21

Note. Logistic regression for male gender with summative predictor variables for A/I symptoms and A/I medication usage; depression is dichotomous.
** p < .05

Table 4.20 Model 3 Summative Predictors Male Gender—Classification Table

		DOCI in C or D (Predicted)		
		No	Yes	% Correct
DOCI in C or D (Observed)	No	40	4	90.9
	Yes	11	7	38.9
Overall % Correct				75.8

Model 4, Summative Predictors, Female Gender

A mirror logistic regression analysis was conducted on the full model within females to evaluate the effect of the A/I symptom sum (interval), A/I medication count (interval), and depression (dichotomous) in Wave A on the likelihood of DOCI in Wave C or D.

Within the female gender, the model was not significant, $\chi^2(3) = 1.66$, $p = .65$, with no individual variable reaching significance (Table 4.21). The variation in the dependent variable explained by the model was even less than males, 2.8% (Nagelkerke R^2). The full model correctly classified subsequent DOCI 69.1% of the time (Table 4.22); sensitivity (ability to classify true positives) was very low (7.4%); and specificity (ability to classify true negatives) was 100%. The model correctly identified DOCI in the two participants predicted; however, the false negative rate is 92.6% and negative predictive value is 68.4%. The model did not identify any significant predictors of subsequent DOCI in females.

Table 4.21 Model 4 Summative Predictors Female Gender—Variables in the Equation

					95% C.I.for EXP(B)	
Predictors	B	S.E.	Sig.	Exp(B)	Lower	Upper
A/I Medication Count	0.41	0.51	.43	1.50	0.55	4.11
Depression	-0.94	1.13	.41	0.39	0.04	3.60
Sum of A/I Symptoms	-0.77	0.72	.29	0.47	0.12	1.89

Note. Logistic regression model for female gender with summative predictor variables for A/I symptoms and A/I medication usage; depression is dichotomous.

Table 4.22 Model 4 Summative Predictors Female Gender—Classification Table

		DOCI in C or D (Predicted)		
		No	Yes	% Correct
DOCI in C or D (Observed)	No	54	0	100.0
	Yes	25	2	7.4
Overall % Correct				69.1

CHAPTER 5

Conclusions, Discussion, and Recommendations

MAJOR FINDINGS AND CONCLUSIONS

This section discussed the major findings of the research questions and the themes extracted from this study.

Specific Aim 1

Evaluate the association between A/I symptoms and subsequent DOCI among participants in the Aging, Demographics, and Memory Study (ADAMS).

RESEARCH QUESTION 1.1

Do cognitively normal individuals with A/I symptoms in Wave A have an increased incidence of DOCI in Waves C or D in comparison to those that did not have A/I symptoms in Wave A?

No association was found between A/I and subsequent dementia for the total sample. However, after evaluating males and females separately, A/I is a significant predictor of subsequent dementia in males. The odds of developing dementia for males was almost five times as high for males with new-onset or worsened A/I, and the risk was more than double. For females, no association was found; in fact, in reviewing the cross-tabulation, the incidence of dementia was lower in women with A/I symptoms in Wave A, not higher.

RESEARCH QUESTION 1.2

Do cognitively normal individuals with anxiety, insomnia, and depressive (A/I/D) symptoms in Wave A have an increased incidence of DOCI in Waves C or D in comparison to those that did not have A/I/D symptoms in Wave A?

The frequencies for the inclusion condition with presence of anxiety symptoms, and insomnia and depression was too low to analyze. As a result, the A/I symptom cluster was evaluated with and without depression. No association was found between A/I+D or A/I-D for the total sample. However, as with Research Question 1.1, a chi-square association with marginal significance was found for males with A/I+D, and statistical significance was found after evaluating the incidence rates and relative risk. The risk of developing dementia was almost four times as high for males with A/I+D.

Specific Aim 2

Evaluate the association between non-BZRA anxiolytic medications or sleep aids (A/I medications) and subsequent DOCI among participants in the ADAMS.

RESEARCH QUESTION 2.1

Do cognitively normal individuals that reported using A/I medications in Wave A have an increased incidence of DOCI in Waves C or D in comparison to those that did not report using A/I medications in Wave A?

No association was found on any of the statistical measures between A/I medication usage and subsequent dementia. This finding was unchanged after controlling for gender separately. Further investigation of the ADAMS dataset, without removing the exclusion variables, found that BZRA usage was not a significant predictor of DOCI in the ADAMS. However, a strong association was found between the A/I medication usage variable and the BZRA usage variables. Given a lack of association between BZRA usage and subsequent DOCI, the failure to find an association between non-BZRA A/I medication

usage and subsequent DOCI is supportive of the original genesis of this research regarding alternative explanations for the association between BZRA usage and subsequent DOCI found in other studies.

Specific Aim 3

Evaluate the association between anxiety, depressive, and insomnia symptoms, the usage of A/I medications, and subsequent DOCI among participants of the ADAMS.

RESEARCH QUESTION 3.1

What is the best set of predictors (A/I medication usage, A/I/D symptoms, gender) from Wave A of developing DOCI in Wave C or D?

No association was found for the full model or for the individual predictors in Model 1 that included all dichotomous symptom variables individually (anxiety, agitation, irritability, depression, and insomnia), A/I medication usage, and gender (See Table 4.15). Small sample size and evidence of multicollinearity issues raise serious concerns regarding the validity of logistic regression approaches. An additional set of logistic regression analyses was conducted using the summed A/I symptom cluster variable in place of the individual variables for anxiety, agitation, irritability, and insomnia and the interval sum of A/I medications reported in Wave A in place of the dichotomous A/I medication usage variable. As with Model 1, the analyses of Model 2 did not find an association with subsequent DOCI for the full model or the individual predictors in the total sample (Table 4.17).

Within gender analyses for females, Model 4, failed to identify any significant predictors (Table 4.21). In males, however, the full model neared significance. As found in Research Questions 1.1 and 1.2, the A/I symptom cluster was a significant predictor of subsequent DOCI in males (Table 4.19). The odds of subsequent DOCI was more than four times higher for male participants with A/I in Wave A.

SUMMARY OF MAJOR FINDINGS

Caution must be used in generalizing the findings of this study. After removing the exclusion variables and participant attrition—from dementia diagnosis on the intake assessment, death, and drop out—the sample size was reduced from the initial 856 participants to only 143. This is clearly inadequate to make any gross generalizations. However, the common thread from the majority of analyses in this study is that there are gender differences in the neuropsychiatric manifestations of prodromal dementia. For example, in Table 4.1, the frequency of males with A/I was higher in those with subsequent DOCI (n = 7) than for males that did not develop DOCI (n = 5). However, the frequency of females with A/I was lower in those with subsequent DOCI (n = 3) than for females that did not develop DOCI (n = 11). If gender differences in the neuropsychiatric manifestations of prodromal dementia are validated in other studies, then this may suggest differences in the patterns of neurodegeneration in men and women.

SYNTHESIS

A/I Symptom Cluster

The findings of this study failed to show any robust association between A/I symptoms and subsequent dementia without accounting for gender differences. The previous studies that identified an association between anxiety (Gulpers et al., 2016; Petkus et al., 2016; Pietrzak et al., 2012) and insomnia (Elwood et al., 2011; Hahn et al., 2014; Kabeshita et al., 2016) and subsequent dementia were conducted on different databases with larger samples sizes. The Beaudreau et al. (2013) study was conducted on the same sample without the exclusions (n = 301) and found a relationship between agitation and subsequent DOCI; but the new-onset or worsened specifier was not used, medical comorbidity was not controlled, and gender differences were not evaluated. Since the exclusion variables were correlated with subsequent DOCI, their inclusion in the

Beaudreau et al. sample skews their findings. While it is unclear whether a larger sample size would enhance the findings of this study, there have been other studies that did not find associations between anxiety and subsequent dementia (de Bruijn et al., 2014; Ramakers et al., 2015).

A/I Medication Usage

The finding that non-BZRA usage was associated with BZRA usage supports the construct validity that non-BZRA usage can be used as a proxy for targeting the symptom cluster targeted by BZRA medications. This study expected to find the association between BZRA usage and subsequent dementia in the ADAMS dataset to be similar to the association Billioti de Gage et al. (2015) reported that indicated a 1.5-2 fold increased risk. The failure to detect an association between BZRA usage and subsequent dementia in the ADAMS dataset could be due to many factors, e.g., smaller sample size, different exclusion/inclusion criteria, differences in the recruitment approaches. If the relationship between BZRA usage and subsequent dementia identified previously (Bellou et al., 2016; Billioti de Gage et al., 2015; Zhong et al., 2015) was due to prodromal symptoms, as suggested in this study, then it is not surprising that A/I was not clearly associated with subsequent DOCI. Subsequent additional analyses utilizing the un-adjusted ADAMS dataset will provide a more robust test on this issue but will reintroduce the confounding variables that will need to be addressed.

Gender Differences

The particular neurodegenerative pattern is what dictates the phenotype expressed cognitively and behaviorally (Nowrangi, 2015). The gender differences identified by this study suggest that, in this sample, males and females expressed different dementia phenotypes. This finding suggests that the pattern of neurodegeneration in dementia may

differ by gender. If that is true, then future dementia studies must evaluate genders separately.

Implications

Healthcare Providers

This study and former research indicates that neuropsychiatric changes may indicate prodromal dementia before the onset of cognitive decline. Without any current cure for dementia or treatment to inhibit the progression, there is no change in practice indicated. However, the knowledge that neuropsychiatric symptoms may indicate a neurodegenerative process is important knowledge for clinicians and all healthcare professionals.

As the research into predictive factors develops and treatments are developed, awareness of the current literature will guide healthcare professionals to provide the best information for patients and families and to provide the most evidence-based practice. The gender differences in dementia phenotype suggested by this study is currently relevant to all healthcare professionals that treat the aging population. The understanding that behavioral changes may vary greatly between genders for the same theoretical illness will help healthcare professionals better approach patients and educate families.

The literature discussed here highlights the debate over BZRA medications and the fear that treatment intended to help people are contributing to a devastating illness. Healthcare professionals need to understand the literature on this topic. While this study does not suggest that BZRA medications should be used in the elderly, changes in practice standards must follow evidence-based recommendations. The prodromal neuropsychiatric symptoms theory is a rational alternative explanation for the correlations identified between BZRA medications and subsequent dementia.

Nursing

Understanding that neuropsychiatric changes are possible indicators of neurodegenerative changes is important for nurses that work with elders, because they may indicate the need for further evaluation or referral. Additionally, a change in personality or behavior may be difficult to understand for families and the nurse; understanding that these changes may have a biological rather than intentional origin may help guide treatment. However, it is important that nurses do not assume dementia and notify patients and families of their suspicions; false knowledge of a currently incurable, progressive illness could be devastating.

General Population

For caregivers who work with the aging population, family members of aging relatives, and the general population, knowledge that neuropsychiatric changes may predict dementia is currently only being studied. Family members and caregivers should not assume that behavioral changes are evidence of dementia, and elders should not engage in self-diagnosis. The findings of this study are currently only in the research realm. Hopefully, with further investigation, researchers will develop treatments and cures for this devastating group of illnesses.

Limitations

Ambiguous Pathology

Dementia is a complex neurodegenerative process that likely has many causes and contributing factors. Additionally, symptoms that we are able to measure are only a proxy for manifestations of an underlying biological process. It is difficult to determine a causal relationship between neuropsychiatric symptoms and neurobiological etiology because there are limitless confounding variables; for instance, anxiety is a normal biological response to environmental stress. This study and others attempt to identify neurobehavioral

manifestations that are differentially more common in individuals with developing dementia than in the general aging population. Neuropsychiatric symptoms, in combination with biomarkers and other predictors, will hopefully lead to earlier identification of individuals with dementia and will contribute to future studies into the prevention and cure of dementia.

Additionally, the NPI survey data is not diagnostic, and the validity of using reported depression instead of a diagnosis is unclear; major depressive disorder (MDD) may yield different results from reported depression. However, because diagnostic syndromes are specific clusters of symptoms, there is no reason to assume that the symptom cluster for a diagnosis—such as MDD—is the same cluster manifest in prodromal dementia. It is likely that the symptoms manifest in prodromal dementia are atypical, because they result from atypical brain processes.

MULTICOLLINEARITY

When the independent variables are correlated with each other, the logistic function is unable to correctly calculate the beta coefficients and standard errors for the predictor variables, because it is unable to separate the individual contributions of the variables (Dormann et al., 2013). In the Beaudreau et al. (2013) study that was conducted on the ADAMS dataset, the authors excluded fewer participants, used the interval score for the NPI, and included two other unrelated predictor variables—education and APOEε4—that would have reduced the multicollinearity problem seen in this study. Additionally, Cummings et al. (1994) reported a significant degree of inter-item correlations within the NPI, so multicollinearity between neuropsychiatric symptoms is known.

The problem of multicollinearity is not unique to this study, because the predictors should be intercorrelated on some level if they predict a single outcome. In this study, the presence of multicollinearity emphasizes the interrelated nature of the variables in the A/I symptom cluster, which is why they were chosen for the cluster. In that sense,

multicollinearity is a given, and a different statistical method should be used. While the low sample size amplified the effect of multicollinearity in the logistic regression analyses in this study, the situation uncovered a, heretofore, weakness not noticed when the samples have been larger that challenges the use of logistic regression. So, studies that have used logistic regression without accounting for multicollinearity should be re-evaluated and more robust analytical approaches, e.g. structural equation analyses or survival analyses, should be employed.

Confounding Variables and Small Sample Size

Because of the varied and uncertain etiology of any specific case of dementia and of the observed symptoms, the potential confounding variables are ambiguous and limitless. This study chose to exclude variables that confound cognitive assessment, neurobehavioral symptoms, and neurocognitive etiology. This approach proved problematic because it reduced the sample size more than expected. It is possible that the exclusion factors were overly exclusive.

A power analysis was not conducted in this study because the dataset had a predefined size. In epidemiological research, there are disease processes that are so rare that they are not identified without very large sample sizes. If there are multiple phenotypes of dementia with differing characteristics, large samples are required to identify the differences.

Strengths

Despite the limitations, the approach used in this study has some strengths. Instead of approaching the investigation by choosing neuropsychiatric symptoms that may predict subsequent dementia, this study chose an identified relationship and selected the symptoms clinically associated with a previously identified predictor variable. BZRA medications are prescribed for specific symptoms and have also been shown to predict dementia. If this

study method were applied to a database with an adequate sample and a demonstrated relationship between BZRA usage and subsequent dementia, the prodromal symptom cluster may prove to be significant. Additionally, this approach should be fairly easy to replicate and would directly target the debate regarding BZRA medications, dementia risk, and prodromal symptoms.

Future Directions

Since the study sample (after removing exclusions) was small, and the goal was to identify prodromal dementia for the purposes of early intervention and preventative research, identification of larger numbers of prodromal dementia cases is more important than determining the best individual predictors. Future studies should focus on a wider umbrella of potential predictors while determining other factors that may help in screening out false positive cases. Triangulating approaches such as biomarkers and protective factors with neuropsychiatric symptoms may enhance early identification of prodromal dementia.

In order to challenge the findings from previous analyses that showed a relationship between BZRA usage and subsequent dementia, such as Billioti de Gage et al. (2014), the study approach presented here should be used to reanalyze the dataset used by the previous authors. While the specific statistical test should be re-evaluated, the concept is presented as follows: a symptom cluster that is shown to correlate with the predictor in question is selected, and the analyses are conducted on the symptom cluster after the predictor is excluded from the sample. This directly challenges the question of whether a predictor is associated independent of the associated symptoms.

The finding that the behavioral phenotype of dementia is different for men and women is both striking and clinically obvious. In addition to the suggestion to study genders separately, the implication that the gender difference also indicates differential neurodegenerative patterns should also be investigated.

Alternative Statistical Analyses

Dormann et al. (2013) reviewed several methods for addressing the problems with multicollinearity. The authors pointed out that there is no way to completely eliminate collinearity in biological research, because the variables used are only proxies of underlying processes. One of the methods discussed involves using proxy symptom clusters. The specific method to use is dependent largely on the variables of interest. For instance, principal components analysis requires interval variables that this study was lacking. Rushing, Sachs-Ericsson, and Steffens (2014) used a combination of structural equation modeling and logistic regression to explore prodromal signs of Alzheimer's dementia in depressed elders. Regardless, this study identified that the statistical method must account for multicollinearity and should analyze genders separately in acknowledgement of the different behavioral phenotypes for men and women.

Triangulation of Approaches

Even for the significant findings, such as A/I symptoms and subsequent dementia in males, the prodromal symptoms only predicted 39% (7/18) of the dementia cases. The goal of future research should be to triangulate the various approaches to maximize the sensitivity with one or more approaches and then to maximize the specificity with one or more other approaches. Qualitative approaches should be used to identify the best set of predictors that can then be tested experimentally. It is unrealistic to think that one method will be able to predict a significant proportion of cases, but by triangulating approaches from difference disciplines, the goal may be possible. The study by Beaudreau et al. (2013) attempted to combine genetic testing and neuropsychiatric symptoms, but the findings were not robust. Combining the study method of Beaudreau et al. (2013) with the EEG and MRI study from Moretti (2015) and the clustering of symptoms described in this study would allow for maximizing both sensitivity and specificity.

Recent advances in genetics through genome-wide association studies (GWAS), such as Seshadri, Fitzpatrick, Ikram, and et al. (2010), have been able to identify risk genes for Alzheimer's dementia and other diseases in certain populations. Instead of conducting these studies on general samples of elders, it is possible to identify dementia phenotypes by combining methodological approaches as described here prior to conducting the GWAS analysis. Triangulating approaches in this way has the potential of combining observable differences with genetics and other types of studies to more accurately classify patients and to identify the true genetic risk factors. The hope is that this information could lead to treatment and prevention.

CONCLUSIONS

The long-term goal is to understand the contributing factors to the development of dementia, with a focus on early identification and prevention. The efforts of this study and the future directions discussed are not aimed at early diagnosis without a solution. Once a reliable method is found to identify persons at risk for developing dementia, those individuals can be studied directly with the goal to prevent the progression to dementia; prevention is more useful than treatment.

This study investigated the idea that the A/I symptom cluster may be a prodromal indicator of developing dementia. Due to an inadequate sample size after employing exclusion variables, the question remains inconclusive. The gender differences identified in this study were not expected and may suggest variant dementia phenotypes for men and women that need further investigation.

Appendix A Person-Time Tables

Person-time is the number of months from the Wave A assessment to the final assessment in either Wave C or D (if Wave D assessment not completed). Incidence rates are the incidence sum divided by the person-time sum.

Table A1 DOCI Incidence for Participants with and without A/I in Wave A

	A/I					
	Male		Female		Total	
Variables	No	Yes	No	Yes	No	Yes
DOCI Frequency	11	7	24	3	35	10
Sum of person-months	3195	770	3195	770	3195	770

Note. Research Question 1.1

Table A2 DOCI Incidence for Participants with and without A/I-D in Wave A

	A/I and Not Depressed					
	Male		Female		Total	
Variables	No	Yes	No	Yes	No	Yes
DOCI Frequency	13	5	25	2	38	7
Sum of person-months	3305	660	4743	625	8084	1285

Note. Research Question 1.2

Table A3 DOCI Incidence for Participants with and without A/I+D in Wave A

	A/I and Depressed					
	Male		Female		Total	
Variables	No	Yes	No	Yes	No	Yes
DOCI Frequency	16	2	26	1	42	3
Sum of person-months	3855	110	5108	260	8963	370

Note. Research Question 1.2

Table A4 DOCI Incidence for Participants with and without A/I in Wave A

	A/I Medication Usage					
	Male		Female		Total	
Variables	No	Yes	No	Yes	No	Yes
DOCI Frequency	17	1	23	4	40	5
Sum of person-months	3613	352	4554	814	8167	1166

Note. Research Question 2.1

Appendix B Medication Variable Lists

Medication lists derived from Stahl (2014).

Table B1 Anxiety Medications

- amitriptyline
- amoxapine
- buspirone
- citalopram
- clomipramine
- clonidine
- cyamemazine
- desipramine
- dothiepin
- doxepin
- duloxetine
- escitalopram
- fluoxetine
- fluvoxamine
- gabapentin
- hydroxyzine
- imipramine
- isocarboxazid
- lofepramine
- maprotiline
- mianserin
- mirtazapine
- moclobemide
- nefazodone
- nortriptyline
- paroxetine
- phenelzine
- pregabalin
- reboxetine
- sertraline
- tiagabine
- tianeptine
- tranylcypromine
- trazodone
- trifluoperazine
- trimipramine
- venlafaxine
- vilazodone

Table B2 Insomnia Medications

- agomelatine
- amitriptyline
- amoxapine
- clomipramine
- desipramine
- dothiepin
- doxepin
- hydroxyzine
- imipramine
- lofepramine
- maprotiline
- mianserin
- nortriptyline
- ramelteon
- suvorexant
- trazodone
- trimipramine

Table B3 BZRA Medications

- alprazolam
- chlordiazepoxide
- clonazepam
- clorazepate
- diazepam
- estazolam
- eszopiclone
- flunitrazepam
- flurazepam
- loflazepate
- lorazepam
- oxazepam
- quazepam
- temazepam
- triazolam
- zaleplon
- zolpidem
- zopiclone

Table B4 Combined A/I Medications Without BZRAs

- agomelatine
- amitriptyline
- amoxapine
- buspirone
- citalopram
- clomipramine
- clonidine
- cyamemazine
- desipramine
- dothiepin
- doxepin
- duloxetine
- escitalopram
- fluoxetine
- fluvoxamine
- gabapentin
- hydroxyzine
- imipramine
- isocarboxazid
- lofepramine
- maprotiline
- mianserin
- mirtazapine
- moclobemide
- nefazodone
- nortriptyline
- paroxetine
- phenelzine
- pregabalin
- ramelteon
- reboxetine
- sertraline
- suvorexant
- tiagabine
- tianeptine
- tranylcypromine
- trazodone
- trifluoperazine
- trimipramine
- venlafaxine
- vilazodone

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Vita

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