

RELATIONSHIPS BETWEEN MEDICATION LEVELS AND DEPRESSIVE  
SYMPTOMS IN OLDER INDIVIDUALS

By

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by

Mohan Krishnan

This work is dedicated to all of the people who have blessed me with their love, helped me find my way, and helped me see the value in the pursuit of wisdom.

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## TABLE OF CONTENTS

	<u>page</u>
ACKNOWLEDGMENTS .....	iv
LIST OF TABLES .....	vii
LIST OF FIGURES.....	viii
ABSTRACT.....	ix
CHAPTER	
1 INTRODUCTION.....	1
2 REVIEW OF LITERATURE .....	4
Depression in Older Individuals.....	4
The Vascular Depression Hypothesis.....	5
Vascular Depression Within a Biopsychosocial Model of Depression.....	7
Polypharmacy.....	9
3 STATEMENT OF THE PROBLEM.....	13
Aim 1. Relationships Among Polypharmacy, Cardiovascular Medication, and Depressive Symptoms.....	14
Aim 2. Relationships Between Medication Effects and Dimensions of Depression .	14
4 METHODS .....	15
Participants.....	15
ACTIVE Pilot Study Participants.....	15
Inclusion and Exclusion Criteria.....	15
Measures .....	16
Interview-Based Measures.....	16
Self-Report Questionnaires.....	16
Procedures.....	17
Categorization of Medications .....	17
Missing Data .....	18
Statistical Analysis .....	19

5	RESULTS .....	20
	Demographic Statistics .....	20
	Medication Statistics .....	20
	Correlational Analysis .....	22
	Aim 1. Relationships Among Polypharmacy, Cardiovascular Medication, and Depressive Symptoms .....	22
	Aim 2. Relationships Between Medication Effects and Dimensions of Depression .....	23
6	DISCUSSION .....	25
	Review of Study Findings.....	25
	Characterization of the Study Sample .....	25
	Aim 1. Relationships Among Polypharmacy, Cardiovascular Medication, and Depressive Symptoms .....	25
	Aim 2. Relationships Between Medication Effects and Dimensions of Depression .....	26
	Synthesis of Findings.....	26
	Implications of Study.....	27
	Detrimental Polypharmacy for Depression.....	27
	Beneficial Effects of Polypharmacy of Cardiovascular Medication for Depression .....	28
	Study Limitations .....	30
	Conclusion .....	33
	LIST OF REFERENCES.....	34
	BIOGRAPHICAL SKETCH .....	39

## LIST OF TABLES

<u>Table</u>	<u>page</u>
5-1 Correlations Among Predictor Variables .....	22
5-2 Regression of Predictor Variables Onto Depression Measures .....	23

## LIST OF FIGURES

<u>Figure</u>	<u>page</u>
1-1 Detrimental and Beneficial Polypharmacy in Depression in Older Individuals.....	2
5-1 Distribution of Participants' CES-D Total Scores .....	21
5-2 Frequency of Occurrence of Different Numbers of Medications Per Participant ...	21

Abstract of Thesis Presented to the Graduate School  
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Polypharmacy, the concurrent usage of multiple medications, is common in older individuals, who often have many health conditions, and can result in detrimental effects including increases in depressive symptoms. However, if polypharmacy in a functional category of medication brings about the successful management of a health concern, such as cardiovascular disease, which itself has a negative impact on mood, that polypharmacy may also actually be beneficial in some circumstances. The present study sought to determine whether overall polypharmacy had the detrimental effect of increasing depressive symptomatology in older individuals, while polypharmacy in the area of cardiovascular medication has the beneficial effect of reducing depressive symptoms, which are hypothesized to have some vascular etiology in many older adults.

Analyses were conducted on data from 165 participants in the ACTIVE Pilot Study (mean age 74 years, 83% female, 55% African-American). A multiple linear regression model, controlling for participant demographics, was used to determine the effects of

polypharmacy on depression. As hypothesized, while overall polypharmacy was associated with increased depressive symptoms, cardiovascular medication was simultaneously associated with a decrease in depressive symptoms.

The findings are consistent with a model of negative polypharmacy effects, representing underlying effects of multimorbidity, increased likelihood of adverse drug reactions, central nervous system dysregulation, or some other process, on depression in older individuals, with a simultaneous beneficial polypharmacy effect for cardiovascular medication, through mechanisms such as a reduction in functional impairment due to cardiovascular disease, or improvement in cerebrovascular functioning.

## CHAPTER 1 INTRODUCTION

The purpose of the present study was to explore relationships between medication levels and self-reported mood in older individuals. Depression, the persistent presence of symptoms such as sadness or loss of pleasure, is observed at elevated rates in frail older individuals, and is a major barrier to enjoying later life. It is a topic of major interest to health care professionals and researchers from many different perspectives. Converging lines of evidence have indicated that mechanisms related to physical frailty, medical multimorbidity, and cardiovascular disease processes may underlie the elevated rates of depression in this population. However, few of these studies have investigated medication burdens related to these conditions and processes, although medication usage is a frequent component of the care regimen for older individuals. To the extent that non-psychological health concerns such as cardiovascular disease may be risk factors for depression in later life, understanding the potentially beneficial impacts of aggressively treating these disorders may be crucial in prevention of depression in this population. On the other hand, if medication regimens, when taken as a whole, have iatrogenic effects, manifested as increased depressive symptomatology, this would represent an additional category of potentially modifiable risk factors for elders' mood disorders.

The current investigation is guided by the conceptual model depicted below, in Figure 1-1, in which polypharmacy may be viewed as composed of both beneficial and detrimental components, related to aspects that are able to manage medical conditions aggressively, and elements that contribute to over-medication.

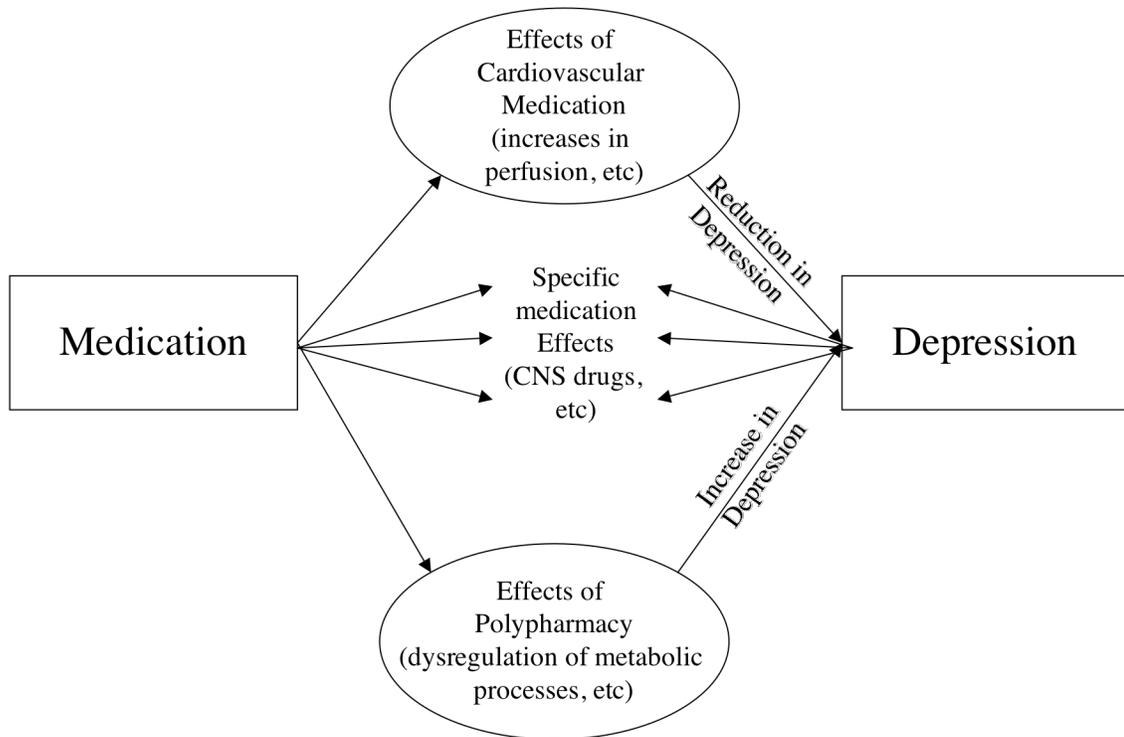


Figure 1-1. Detrimental and Beneficial Polypharmacy in Depression in Older Individuals

The current investigation sought to expand the body of research on the effects of multimorbidity and cardiovascular disease on depression in older individuals, by investigating the role of general medication burden, and of medication management of cardiovascular disease, on the presence of depressive symptoms in older individuals. It was hypothesized that elders who take large numbers of medications, overall, would be likely to show more signs of depression, but that those who receive more cardiovascular medications, within the context of a polypharmacy regimen, would, in turn, be less likely to show signs of depression.

These hypotheses have implications for our collective understanding of the etiologies of depression in older individuals, and the possible relationship between depressive symptoms and cardiovascular disease. It also has implications for prevention and treatment of depression in the elderly, stressing the need for screening of depression

in the context of evaluation for cardiovascular disease, and integration of services aimed at improving psychological and physiological functioning.

In the subsequent chapters, an overview is provided of the existing body of literature on the causes and progression of depression in older individuals, as well as the impacts of general medication burden, followed by the aims, design, and results of the present study. The results will then be analyzed and synthesized, and the limitations of the present study will be considered. Finally, the contribution of this work to the study of depression in older individuals will be summarized.

## CHAPTER 2 REVIEW OF LITERATURE

### **Depression in Older Individuals**

Improving quality of life for older individuals is a common goal for many health care professionals (Borowiak & Kostka, 2004; Boyd et al., 2005). While this is broadly true of health care for all populations, it is particularly important when working with older individuals, because of the impacts of medical multimorbidity and the onset of physical frailty (Gijssen et al., 2001; Mitnitski et al., 2002).

In addition to physical frailty and illness, research has also examined mental illness in late life, with a particular emphasis on depression (Blazer & Hybels, 2005). Two arguments initially posited that true depression would be rare in later life. One argument made in favor of this view was that the ability to self-regulate negative affect, and to selectively interact with the environment in such a way as to maintain affective balance, were skills that continued to develop over the course of the lifespan, and that older individuals would be more proficient at these skills, and thereby less susceptible to depression, than their younger counterparts (see, for instance, Consedine & Magai, 2003). Another argument was that perceived depression in older individuals is primarily the result of somatic complaints such as “aches and pains,” and does not truly represent the syndrome of depression (see, for instance, the discussion in Blazer et al., 1998). However, subsequent research has found that these explanations are not satisfactory in describing the range of mood experiences of older individuals, that some older individuals do indeed experience depression as it is traditionally conceived of, and that

this depression is not purely limited to the experience of somatic complaints (Blazer et al., 1998).

This line of research indicated that the affective characteristics of depression in older individuals are approximately comparable to depression in younger adult populations, but studies also indicated vastly different rates of depression in certain sub-populations of older individuals. This research indicated that, in community samples, base rates are comparable to community samples of younger adults, but that in clinical and institutional settings, they are substantially higher, with particularly high rates among patients being seen for cardiovascular concerns and individuals in long-term care facilities, which house frail older individuals more likely to have increased medical comorbidities (Kramer, 1988; Parmalee, 1989; Rapp, 1988; Taylor et al., 2004). In addition, studies have indicated that physical and mental complaints are particularly likely to co-occur in later life. For instance, one study indicated that, among elderly individuals receiving inpatient treatment for depression (with a mean age of 76.2 years), more than 75% had at least one comorbid general medical condition, and almost half had two or more, most commonly cardiovascular conditions such as hypertension and atherosclerosis (Proctor et al., 2003).

### **The Vascular Depression Hypothesis**

This pattern of high rates of depression among clinical populations and older individuals with high levels of multi-morbidity, particularly in the area of cardiovascular conditions, inspired the vascular depression hypothesis as an explanation for depression in later life. This hypothesis stated that this form of depression might be the manifestation of underlying neuropathology caused by cerebrovascular deficit (Alexopoulos, 1990). This hypothesis was validated both by neuro-imaging and by postmortem techniques,

which found evidence of white matter pathology in depressed individuals who were above the age of 60, but not in younger depressed individuals or non-depressed elders (Krishnan et al., 1997). It was also validated by retrospective analyses of risk, which found substantially increased rates of the development of depression in individuals who had histories of risk factors for stroke or heart attack such as high blood pressure or cholesterol, diabetes mellitus, or a history of smoking (Mast et al., 2004; Oldehinkel et al., 2003). Krishnan et al. (2005) extended this research by demonstrating that, not only did cardiovascular risk predict the onset of depression, but that depression was a prominent indicator of the disease pathway leading to stroke, with individuals who had similar cardiovascular risk histories much more likely to experience stroke if they first developed depression than if they did not.

Taken together, this research indicates that, within the population of older individuals, there may be unique neuropathological factors related to cardiovascular health that help explain some cases of depression as part of a process which begins with cardiovascular risk burden, progresses to cerebrovascular deficit, white matter pathology, and concomitant depression, and eventually leads to an increased risk of stroke. The exact mechanisms behind this process are not understood. Research has indicated that patterns of vascularization of cerebral white matter may lead to areas, called “watershed areas,” in which small vessels are responsible for blood provision, that these small vessels may be more vulnerable to the early effects of reduced vascular performance, leading to increased vulnerability of specific regions of white matter, and that this process may be an intermediate step in the development of cerebrovascular deficit that leads to strokes (Inzitari, 2003; Pantoni & Garcia, 1997).

### **Vascular Depression Within a Biopsychosocial Model of Depression**

The pattern described by research in vascular depression is not likely to underlie all cases of depression beginning in late life, or to completely explain the prevalence of late-life depression even within a specific individual. Rather, it must be considered as a component of a biopsychosocial model of depression. Depression in later life is likely to be determined by multiple factors, just as it is during other phases of life. One contribution is likely to be that of stressful life events. Some researchers have proposed that these have a cumulative burden in increasing the likelihood of depression, leading to increased risk in older individuals, purely by virtue of a longer life in which to experience stressful life events (O'Sullivan, 2004). While studies have provided some support for this hypothesis, and have identified certain stressful life events, such as the loss of a partner or a grandchild, as being particularly associated with depression in late life, they have found modest overall increases in depression as a result of these types of life events (Lindeboom et al., 2002). Another contributing factor is likely to be individual differences in personality characteristics. Although researchers, as previously implicated, have theorized that older individuals have better affective regulation, personality characteristics such as neuroticism appear to play a role throughout the lifespan, and may contribute to risk for depression (Consedine & Magai, 2003; Blazer & Hybels, 2005). Finally, there are also likely to be other genetic and biological substrates for depression in older individuals. One of these factors is likely to be the role of hormonal processes. Some studies have indicated that estradiol hormone therapy may have beneficial impacts on depressive symptoms (Dennerstein et al., 1979). Estrogen has also been identified as a neuroprotective agent, with possible protective capabilities in the damage process associated with stroke ischemia, although this research has been equivocal (Gibson et al.,

2006; Green & Simpkins, 2000). This suggests that estrogen and related hormones might not only have independent roles in the development and maintenance of depression, but may also have roles in the process underlying vascular depression. Other hormones, including stress hormones, such as cortisol, may also play an important role in depression throughout the lifespan (Blazer & Hybels, 2005). Another of these factors is likely to be the contribution of the serotonin transporter gene, and particularly the region of this gene known as 5-HTTLPR, which has been implicated in the development, maintenance, and prognosis of depression in late life (Lenze et al., 2005). These factors may also interact to produce additional risk for depression. For instance, researchers have demonstrated that individuals homozygous for one version of the 5-HTTLPR allele are at greater risk for developing depression in the wake of stressful life events than individuals expressing other genotypes (Wilhelm et al., 2006).

Within this biopsychosocial model, however, vascular etiology appears to play an important role in understanding depression that is unique to the population of older individuals. Research in support of the vascular depression hypothesis has many limitations. It has not yet been able to demonstrate explicitly that white matter deficits are the cause depression in later life. It also has not been able to fully explain the underlying neuropsychological basis for mood disturbances given this type of neuropathology. It should also be noted that, while the vascular depression hypothesis considers a course in which depression follows sub-acute cardiovascular conditions (e.g. those which may not be immediately life threatening), there are also bi-directional relationships between depression in older individuals and acute cardiovascular events. These relationships are not limited to the context of stroke, as discussed above, but also include elevated rates of

depression in individuals recovering from myocardial infarctions and increased risk for potentially fatal ventricular arrhythmias in depressed individuals (Ziegelstein, 2001; Whang et al., 2005).

Nonetheless, this mechanism provides interesting insight into the interactions among physical health, specifically cardiovascular health, the brain, and mood, and provides a possible neurobiological basis for some cases of depression in later life.

### **Polypharmacy**

While the research on vascular depression suggests a very specific relationship between vascular comorbidities and the development of depression, a body of research has also grown that demonstrates substantially more general correlates between multimorbidity and cognitive functioning. Many of these effects are studied through the phenomenon of polypharmacy, wherein elderly individuals are likely to take a large number of different medications, frequently prescribed and managed by different physicians and pharmacists, who may not have opportunities to communicate fully with each other (Kingsbury et al., 2001). Polypharmacy can be measured as simply the total number of prescription drugs an individual takes.

Rollason & Vogt investigated research in polypharmacy and concluded that 38-52% of individuals in the US over the age of 65 take more than five different prescriptions, and that an individual is likely to take 0.4 more prescriptions per decade of age (2003). Beyond multimorbidity, patient and healthcare provider attitudes were also cited as potential explanations for this phenomenon. Furthermore, Veehof et al. investigated longitudinal polypharmacy in older individuals, and found that, particularly for those individuals for whom the number of medications increased rapidly over time,

clear indications for additional medications, based on changes in disease severity or new diagnoses, were frequently absent (2000).

While this method of characterizing the medication burden is very simplistic, researchers have nonetheless been successful in demonstrating that polypharmacy, measured in this way, is a predictor of a variety of concerns, including an increased likelihood of falls, delirium, and reduced cognitive performance, and have also implicated polypharmacy as an independent cause both of general adverse health events and increased mortality (Field et al., 2001; Flaherty et al., 2000; Hogan, 1997; Klarin et al., 2005; Mamun et al., 2004; Sloane et al., 2002; Starr et al., 2004; Weiner et al., 1998).

Polypharmacy can be conceptualized as arising from a number of different mechanisms. The most basic explanation for polypharmacy is that an individual takes more medications because they have more health conditions. In this model, multimorbidity is a cause of polypharmacy, and detrimental effects such as those seen above are not particularly surprising, since these kinds of broadly negative outcomes are often seen in individuals struggling with multiple serious medical conditions. A second model that helps to explain adverse events such as those described above is that, as the medication burden increases, individuals seem to be more likely to receive medications for multiple conditions from multiple health care practitioners, who are not necessarily in close communication. In such a situation, the chances of inappropriate prescription increases, including the initiation of medications that are likely to have adverse impacts, either due to the frailty of ill older individuals, or through interactions with other concurrently prescribed medications. A second possible impact of this model is the prescription of medication for symptoms that are misunderstood because of a lack of

knowledge about existing medications and already diagnosed conditions, leading to excess medication for which there is no medical indication, which may lead to unpredictable changes in areas such as neurochemical or endocrine functioning. Indeed, studies have shown at least preliminary support for both of these models, indicating that the likelihood of adverse drug events and adverse drug-drug interactions do increase with polypharmacy in older individuals, and that older individuals who have high medication burdens are more likely to have one or more medications for which no clear medical justification is documented (Hogan, 1997; Veehof et al., 2000).

At the same time, since the basis for medication is not only the treatment of symptoms, but also the amelioration or prevention of serious medical conditions, a third important model of polypharmacy's effects is that increased polypharmacy represents aggressive treatment of general medical conditions, which should lead to reduced negative impacts of multimorbidity and may play a beneficial role. Particularly in the area of cardiovascular disease, many disease processes are often effectively managed in early phases through aggressive treatment with medication, such as with the use of angiotensin-converting enzyme inhibitors (ACE Inhibitors) in the case of congestive heart failure, as well as medication-based management of related risk factors, such as hypertension (Rich, 2005). Successful medication-based management can be an indicator of early response, averting the need for hospitalization and more serious interventions, such as cardiovascular bypass surgeries, with which a greater likelihood of adverse outcomes and risk are associated.

While some discussion of this hypothesis, sometimes referred to as "beneficial polypharmacy," has taken place, few studies have demonstrated support for this

hypothesis, although researchers have begun to identify situations in which this model might apply, such as combination drug therapies of conditions such as psychotic disorders and, importantly, the treatment of cardiovascular conditions (Cleland et al., 2000; Kingsbury et al., 2001). In these cases, polypharmacy was seen to be associated with positive outcomes that were related to the aggressiveness of prevention and treatment of identified conditions or risk factors.

### CHAPTER 3 STATEMENT OF THE PROBLEM

The present study seeks to address these questions by examining relationships between the number of medications an individual uses, both as a whole, and within functional categories, and the symptoms of depression in a community sample of healthy older individuals.

The usage of a community sample is important for a study of this kind. While rates of clinical depression will tend to be low in healthy community samples, rates of subsyndromal depression, or the presence of symptoms of depression that do not meet the full criteria for a diagnosis of Major Depressive Disorder, are substantial (VanItallie, 2005). Although there is some controversy over the measurement or conceptualization of subsyndromal depression, research has shown that it is a serious concern, both as a risk factor for Major Depressive Disorder and as a predictor of related negative outcomes such as perceived disability, increased utilization of medical services, and increased risk of suicide (Chopra et al., 2005; Johnson et al., 1992). Specifically in the context of older adults, minimal symptoms of depression, as measured by sub-clinical elevations in self-report depression inventories, have been found to be strong indicators of adverse events, such as myocardial infarction (Bush et al., 2001).

Furthermore, given that rates of depression are high in institutional populations of older individuals, but low in the community, many individuals who are institutionalized and depressed are likely to have previously been community-dwelling and experiencing reduced levels of depression. The ability to detect a relationship between cardiovascular

medication regimens and depressive symptomatology prior to the onset of clinically significant depression might therefore allow researchers to explore the possibility of preventative measures. This is particularly critical if, as the vascular depression hypothesis suggests, some cases of depression in late life are the result of organic neuropathology, which is irreversible.

To begin to address these questions, in the present study, we address the following three aims.

**Aim 1. Relationships Among Polypharmacy, Cardiovascular Medication, and Depressive Symptoms**

We hypothesize that, when demographics and the use of hormones, antidepressants, and other central nervous system medications are controlled for, polypharmacy will be associated with increased depressive symptoms, but that cardiovascular drugs will be associated with reduced depressive symptoms. We hypothesize that these are independent, simultaneously observable effects in opposite directions.

**Aim 2. Relationships Between Medication Effects and Dimensions of Depression**

Since, as discussed above, previous research has implicated somatic complaints due to physiological conditions as a source of apparent depressive symptomatology, and warned that somatic complaints may not truly represent depression in the elderly, we further hypothesize that these effects will exist not only for the somatic dimension of depression, but also in other dimensions of depression. Stated in another way, polypharmacy and cardiovascular medication levels will be predictors of not only the overall level of depressive symptomatology, but also of multiple aspects of depression, not limited to somatic complaints.

## CHAPTER 4 METHODS

### **Participants**

#### **ACTIVE Pilot Study Participants**

Data from the Pilot Study of the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) project were analyzed. The ACTIVE study is a randomized clinical trial of targeted cognitive interventions, attempting to determine if cognitive training can produce persistent improvements in the cognition of older adults, and if these improvements lead to benefit in everyday life (Ball, 2002). In preparation for this study, a smaller, non-longitudinal study was conducted to investigate psychometric properties of the proposed instruments, to assess the ability to recruit participants to the trial, and to test the feasibility of using the ACTIVE protocol with diverse populations. This study was conducted on a community-based sample from six sites in the Northeast, Southeast and Midwest United States.

#### **Inclusion and Exclusion Criteria**

Inclusion criteria for the study consisted of women and men aged at least 65 years old, who had no functional disabilities at the beginning of the study, and a Mini-Mental Status Examination (MMSE) score above 23. Individuals were also excluded if they had a self-reported recent history of stroke, cancer or dementia diagnoses. A total of 168 participants were enrolled in the study.

## **Measures**

### **Interview-Based Measures**

Participants' demographic information and an assessment of their depressive symptomatology were obtained in a phone-based interview. In addition to age, the information recorded for each participant included gender, years of education, and race. In addition, although a detailed checklist of prior health conditions was not available, participants' cardiovascular risk was estimated by participant self-reported diagnosis of Diabetes or Heart Disease (0, 1 or 2 total conditions).

During a subsequent in-person interview, a "brown-bag audit" of medication was performed. This consisted of each participant bringing all medications they were currently taking at the request of a health care provider (both over-the-counter and prescription medications) to an interview. Medications provided during the audit were documented by the interviewers. This method has been shown to be effective in accurately portraying the medication status of older individuals (Caskie & Willis, 2004). Medications were recorded by either brand or generic name, along with dosage route, and frequency (or "as needed" status). All medications were later standardized into therapeutic classes, as discussed in the Procedures section, below.

### **Self-Report Questionnaires**

Depression was assessed using the Center for Epidemiological Studies Depression Scale (CES-D(20)), a robust measure of depression that has been validated in adults, including different age groups and races (Blazer et al., 1998; Wallace & O'Hara, 1992; Weissman et al., 1977). This scale has a four-factor structure, consisting of Somatic Complaints (such as sleep disturbance), Depressive Affect (feelings of sadness or loneliness), Positive Affect (the absence of feelings of happiness or joy), and

Interpersonal Problems (the belief that others are unfriendly or dislike the individual), and also provides a Total Score that represents overall depressive symptomatology (Blazer et al., 1998; Roberts, 1980). While the CES-D total score can be compared to a cut-off score (typically 16) to determine if an individual is clinically depressed, the majority of individuals in this sample had low levels of depression, and so the actual score was used instead of a diagnostic classification, a technique that has been used with this instrument in the past, and has been effective in demonstrating the effects of minimal symptoms of depression (Wallace & O'Hara, 1992).

## **Procedures**

### **Categorization of Medications**

After collection of medication information by interviewers, the medications were coded into American Hospital Formulary Service (AHFS) classifications, a functional classification that is widely used in the health care professions (McEvoy, 1996) by researchers from the ACTIVE team. This formulary system provides hierarchical classification of medications into broad functional categories (such as central nervous system agents), as well as sub-classification into smaller functional categories (such as anxiolytics), and therefore allows for analysis at multiple functional levels.

The number of drugs each participant took in several categories of interest was then determined. The first of these categories consisted of medications used in response to cardiovascular disease, formed from drugs in AHFS groups 20 (blood formation and coagulation), 24 (cardiovascular drugs) and 40 (Electrolytic, Caloric, and Water Balance). The numbers of different drugs in the relevant classes were summed to arrive at this variable. These three functional categories were pooled together because all drugs in

these categories are commonly prescribed for the management of cardiovascular conditions.

The number of drugs with primary central nervous system impacts (Group 28) was also determined, in a similar fashion, with one subcategory, antidepressants, considered separately, since, as previously indicated, drugs in these functional categories are likely to have impacts on mood. Hormones and synthetic hormones (Group 68) were also included in the analysis, since they have been implicated to have impacts both on mood and on cardiovascular functioning.

Finally, the overall level of polypharmacy was computed as the number of different drugs, irrespective of therapeutic class, for each participant. This variable included contributions from the specific classes of drugs discussed above.

### **Missing Data**

If a participant had missing data for two or fewer items on the CES-D, mean scores were used to impute missing data (one participant was dropped for this reason); participants with more than two items missing were excluded from subsequent analysis, due to concerns of excessive distortion of the CES-D profile due to imputation of missing responses from a limited number of available responses. For the computation of the CES-D Total Score and its two larger subscales (the Somatic Complaints subscale and the Depressive Affect subscale) missing items from the measure were replaced using mean substitution. However, the remaining two subscales, Positive Affect and Interpersonal Items, contain few items from the CES-D, and could be distorted considerably by mean substitution; as a result, participants with missing values were excluded from analyses using those two subscales as the dependent variable (relevant numbers of valid participants are presented along with the results of these analyses). Two participants for

whom medication data was not available (two participants) were also removed from subsequent analyses. The final number of participants included in the main analyses was 165.

### **Statistical Analysis**

Demographic statistics were computed, and a linear regression was performed for the CES-D total score against demographics, cardiovascular risk, the levels of CNS, antidepressant, hormonal and cardiovascular drugs, and the overall level of polypharmacy. The predictors were entered in blocks into this regression, with demographics and risk burden entered first, to control for the overlapping effect of these variables and the medication variables of interest. Then, specific categories of drugs were entered in the second block, to determine if these had an impact on mood above and beyond demographics. Finally, polypharmacy was entered in the third block, to determine if this had an additional impact that was distinct from the impact of medication in the functional categories. The regression model was then repeated for each of the four subscales of the CES-D.

## CHAPTER 5 RESULTS

### **Demographic Statistics**

For the 165 participants remaining after removal of individuals due to missing data concerns, the mean age at the time of the study was 73.7 years (SD = 6.1), and 83% were female. 55% of participants were African American, while the majority of the remainder (42%) were European American. The mean education level was 12.1 years (SD = 3.0).

While few individuals in the sample endorsed a sufficient number of CES-D items to meet the criteria for clinical depression (a total score of at least 16 points; 9% of the sample endorsed this level of depressive symptomatology), the vast majority (86%) of participants did endorse at least one symptom of depression. Figure 5-1 summarizes the distribution of observed CES-D Total Scores, indicating the number of individuals endorsing a clinically significant severity of depressive symptoms, as well as individuals endorsing lesser levels of depressive symptoms, divided at arbitrary cut-points (0-4, 5-8, and 9-15 total points). Most participants (78%) endorsed one or more somatic complaints (e.g. sleep or appetite disturbances), while fewer (43%) endorsed depressive affect (e.g. sadness or loneliness), a lack of positive affect (e.g. the absence of happiness or enjoyment; 46%), or interpersonal symptoms (e.g. perception of others as unfriendly; 12%).

### **Medication Statistics**

The mean number of medications per participant in the sample was 2.9, with 20.6% of participants taking five or more medications, and only 13.9% reporting no current

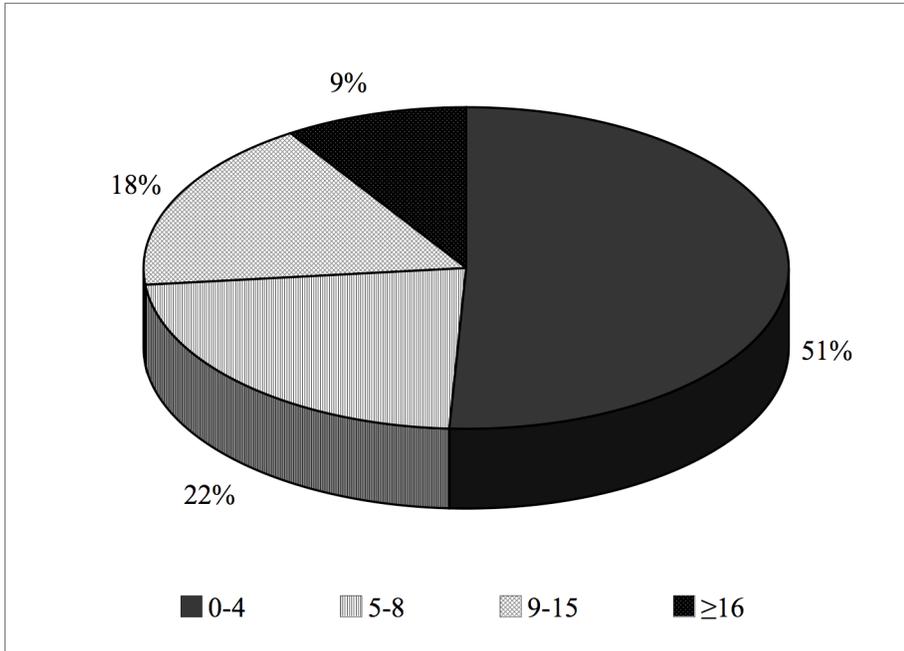


Figure 5-1. Distribution of Participants' CES-D Total Scores medications.

Figure 5-2 depicts the distribution of overall numbers of medications for participants.

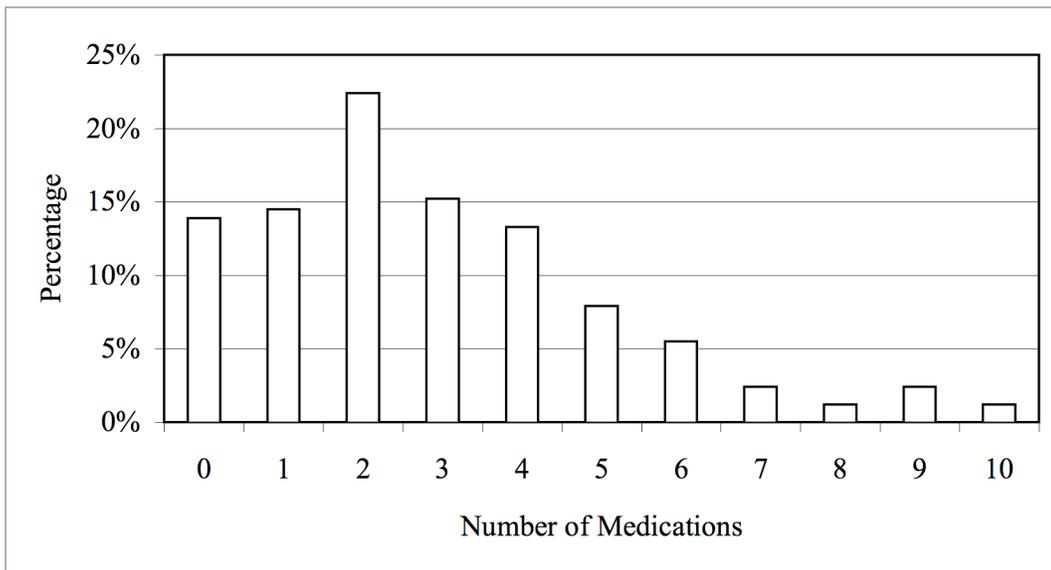


Figure 5-2. Frequency of Occurrence of Different Numbers of Medications Per Participant

The most frequently endorsed categories of medications included Cardiovascular; Hormones; Electrolytic, Caloric, and Water Balance; Central Nervous System; Gastrointestinal; and Blood Formation.

### Correlational Analysis

Correlations among the predictor variables are shown in Table 5-1, with correlations significant at the  $p < 0.05$  level shown in boldface. Notably, an increased number of cardiovascular conditions from the screening instrument (which does not necessarily represent all possible cardiovascular conditions) was associated with taking fewer cardiovascular medications, as well as with fewer hormone medications.

Polypharmacy was significantly associated with a greater number of Cardiovascular, Central Nervous System, and Hormone drugs.

Table 5-1. Correlations Among Predictor Variables

	1	2	3	4	5	6	7	8	9	10	11
1. Age (years)	1.00										
2. Gender	0.04	1.00									
3. Education	<b>-0.19</b>	-0.07	1.00								
4. Race = White	<b>0.28</b>	<b>-0.17</b>	0.02	1.00							
5. Race = Other	0.05	-0.11	0.09	-0.15	1.00						
6. CVRFs	0.00	0.02	<b>0.22</b>	0.10	-0.05	1.00					
7. Cardiovascular Drugs	-0.02	-0.01	-0.12	-0.09	0.06	<b>-0.53</b>	1.00				
8. CNS Drugs	0.00	0.01	<b>-0.24</b>	-0.04	0.02	-0.13	-0.05	1.00			
9. Anti-Depressants	-0.03	0.08	-0.09	-0.01	-0.03	0.01	-0.01	0.07	1.00		
10. Hormones	-0.04	-0.01	-0.10	-0.01	-0.01	<b>-0.31</b>	0.12	0.09	0.04	1.00	
11. Polypharmacy	-0.02	0.04	<b>-0.23</b>	-0.09	0.09	<b>-0.57</b>	<b>0.77</b>	<b>0.35</b>	0.12	<b>0.47</b>	1.00

Note: Correlations significant at the  $p < 0.05$  level are boldfaced. Abbreviations: CVRFs - Cardiovascular Risk Factors; CNS Drugs - Agents acting primarily on the Central Nervous System

### Aim 1. Relationships Among Polypharmacy, Cardiovascular Medication, and Depressive Symptoms

The linear regression of total CES-D score on the predictor variables is described in Table 5-2. The overall model was significant ( $F(11, 153) = 3.270, p < 0.001$ ), and described 19% of the variance in CES-D score. Of this, 12.7% of unique variance, above and beyond demographic variables, was described by the discrete drug categories, and an

additional 4.6% of variance was associated with polypharmacy, above and beyond the individual effects of the drug categories and demographics. An increase in the number of cardiovascular drugs was associated with a decrease in depressive symptoms ( $\beta = -0.447$ ,  $p = 0.007$ ; regression weights reported as standardized unless otherwise noted), as was an increase in the number of hormonal drugs ( $\beta = -0.237$ ,  $p = 0.025$ ); an increase in overall polypharmacy was also separately associated with a substantial increase in depressive symptomatology ( $\beta = 0.610$ ,  $p = 0.004$ ). No other variables reached significance as predictors in this model.

Table 5-2. Regression of Predictor Variables Onto Depression Measures

Parameter	Standardized Regression Coefficients*				
	CES-D Total Score	Somatic Complaints	Depressive Affect	Positive Affect	Interpersonal Problems
Age (0=below median)	0.136	0.166	0.072	0.050	0.040
Gender (1=female)	0.024	0.044	0.021	0.001	0.065
Education (years)	-0.052	-0.096	0.032	-0.037	-0.071
White race (1=true)	-0.047	-0.101	0.040	-0.010	-0.096
Other race (1=true)	-0.096	-0.063	-0.119	0.017	-0.056
# of CVRFs	-0.149	-0.011	-0.083	<b>-0.273</b>	-0.071
Cardiovascular Drugs	<b>-0.477</b>	-0.267	<b>-0.716</b>	0.048	-0.396
Other CNS Drugs	0.008	-0.010	-0.149	<b>0.236</b>	-0.080
Anti-Depressants	0.088	<b>0.154</b>	0.072	-0.023	-0.076
Hormone Therapy Drugs	<b>-0.237</b>	-0.162	-0.331	0.000	-0.211
Polypharmacy	<b>0.610</b>	<b>0.503</b>	<b>0.904</b>	-0.225	<b>0.513</b>
Valid n**	165	165	165	154	160
Cumulative R <sup>2</sup>	0.190	0.187	0.180	0.098	0.078
Model F	3.270	3.191	3.046	1.405	1.133
Model Significance	0.001	0.001	0.001	0.177	0.078

Notes: (\*) Regression coefficients result from five separate linear regression models for the total CES-D score and the four sub-scales. Boldfaced coefficients were significant at the  $p < 0.05$  level. (\*\*) For the four subscales, missing values were not imputed due to the small number of items on each scale, reducing the number of valid cases. Abbreviations: CVRFs - Cardiovascular

## Aim 2. Relationships Between Medication Effects and Dimensions of Depression

The results of the regressions for the four subscales of the CES-D are also presented in Table 5-2, above. The model for the Somatic Complaints subscale was

significant ( $F(11, 153) = 3.191, p = 0.001$ ), and described 18.7% of the variance in the subscale. In this model, increasing age was associated significantly, but slightly, with increased Somatic Complaints ( $\beta = 0.166, p = 0.036$ ), as was a larger number of Anti-Depressant medications ( $\beta = 0.154, p = 0.044$ ), and, more substantially, an increase in overall polypharmacy ( $\beta = 0.503, p = 0.016$ ). The model for the Depressive Affect subscale was also significant ( $F(11, 153) = 3.046, p = 0.001$ ), describing 18% of the variance in Depressive Affect. 11 additional participants were excluded from the analysis, due to missing responses on this subscale of the CES-D, leading to a total of 154 participants in the analysis. An increased number of cardiovascular drugs was strongly associated with decreased Depressive Affect ( $\beta = -0.716, p < 0.001$ ), as was an increased number of Hormone drugs, albeit at a weaker level ( $\beta = -0.331, p = 0.002$ ). At the same time, an increase in overall polypharmacy was strongly associated with an increase in Depressive Affect ( $\beta = 0.904, p < 0.001$ ).

The model for Positive Affect, on the other hand, failed to reach significance ( $F(11, 142) = 1.405, p = 0.177$ ). Five additional participants were excluded from this analysis due to missing data on this subscale of the CES-D, leading to a total of 160 participants in this analysis. However, the number of co-morbid cardiovascular conditions was mildly associated with a reduction in this dimension of depression ( $\beta = -0.273, p = 0.008$ ), and the number of CNS medications, not including anti-depressants, was mildly associated with an increase in this dimension of depression ( $\beta = 0.236, p = 0.048$ ). The model for Interpersonal Problems also failed to reach significance ( $F(11, 148) = 1.133, p = 0.340$ ), although overall polypharmacy was moderately associated with increases in this dimension of depression ( $\beta = 0.513, p = 0.044$ ).

## CHAPTER 6 DISCUSSION

### **Review of Study Findings**

#### **Characterization of the Study Sample**

The percentage of clinically depressed individuals (9%) in the present sample compares favorably with that reported in a racially similar sample by Blazer et al. in which a rate of clinically significant depression, as assessed by the CES-D, of 9% was also found for community-dwelling elders above the age of 65 (Blazer et al., 1998). At the same time, the mean number of medications per participant (2.9) was approximately comparable to that reported by Veehof et al. (2000) for a similar age cohort in the Netherlands (2.6 drugs per participant, at study onset, for a population with mean age 73 years), although somewhat lower than that reported for some other studies (Rollason & Vogt, 2003). Differences between these studies may have been driven by broader inclusion in some epidemiological studies – the ACTIVE study did not include participants who were community-dwelling, for instance, but functionally impaired. However, taken as a whole, these findings indicate that the study sample is approximately comparable, along the dimensions of depressive symptomatology and medication usage, to other studied samples that are similar in age and/or racial demographics.

#### **Aim 1. Relationships Among Polypharmacy, Cardiovascular Medication, and Depressive Symptoms**

In the present study, overall polypharmacy was significantly associated with increased depressive symptoms, as measured by the CES-D Total Score, even when

controlling for demographics, cardiovascular risk, and specific categories of drugs likely to be related to depressive symptoms. At the same time, independently of the effect of overall polypharmacy, the use of cardiovascular medications had a unique effect, associated with reduced depressive symptoms, as measured by the CES-D Total Score, providing support for the hypothesis that independent and opposing effects of beneficial and detrimental polypharmacy impacts would be observable in the context of depressive symptomatology.

### **Aim 2. Relationships Between Medication Effects and Dimensions of Depression**

When the detrimental impact of polypharmacy on depression was considered within specific dimensions of depression represented in the CES-D, this effect was not limited to the Somatic Complaints subscale of the CES-D, but was also present in the Depressive Affect subscale, indicating that this effect existed in the context of the core mood symptomatology of depression, as opposed to the existing solely as a projection of somatic complaints due primarily to a general medical condition on the measure of depression.

When the beneficial impact of cardiovascular medication was considered in the context of the dimensions of depression, the effect was found to be primarily represented in the Depressive Affect subscale, again demonstrating a link between the impacts of medication and the core mood symptoms of depression.

### **Synthesis of Findings**

The pattern of results presented above is consistent with the notion of simultaneous overall detrimental impact of polypharmacy and beneficial impact of polypharmacy in the case of cardiovascular medication, for the symptoms of depression, in older individuals, although it is important to note that causation cannot be inferred either from

this relationship or from the relationship between cardiovascular medication and increased depressive symptoms, and that overall polypharmacy cannot be made truly independent of cardiovascular polypharmacy. This model of simultaneous detrimental and beneficial polypharmacy is consistent with the hypothesized model presented earlier, in Figure 1-1.

### **Implications of Study**

#### **Detrimental Polypharmacy for Depression**

There are a number of possible explanations for the observed detrimental impact of polypharmacy. Overall polypharmacy might lead to increased dysregulation of neurotransmitters or endocrine processes, leading to adaptation difficulty. This may proceed through a generalized route that involves cumulative effects of many drugs in a non-specific way, particularly the unexpected impacts of drugs that are prescribed for inappropriate reasons, or it may proceed through the increase in the likelihood of specific adverse drug-drug interactions (Hogan, 1997; Veehof et al., 2000). Further understanding of these mechanisms may lead to more effective intervention strategies for older individuals with co-morbid cardiovascular disease and depressive symptomatology.

It is also possible that the detrimental effect of polypharmacy is mainly an effect of multimorbidity, and not of the medication itself (i.e. the presence of multiple medications serves as a proxy for the presence of multiple underlying medical conditions).

Differentiating this alternative explanation from a mechanism rooted in the effects of polypharmacy on the central nervous system is difficult because no clear method exists whereby the number and strength of medications can be meaningfully scaled by the number and severity of the medical disorders that necessitate the medications in the first place. Moreover, in this study, measurement of health conditions was not adequate to

permit the independent assessment of physical health conditions at the same level of detail as was achieved in analysis of the available medication data. As previously indicated, medication prescribed without clear indication is a serious concern within observed polypharmacy, and partitioning its effect from the effect of additional medications prescribed with clear indications may be important in understanding the mechanism of polypharmacy's deleterious effects.

In either event, the suggestion that polypharmacy may carry affective concomitants in the form of increased symptoms of depression adds to a growing body of literature supporting the need for interdisciplinary interventions to attempt to reduce polypharmacy in older individuals, without compromising the efficacy of treatment of the diagnosed disorders for which they are being treated. Research on the benefits of such interventions has focused primarily on cost savings, to date (Christensen et al., 2004). However, such interventions already appear to be able to identify and act on individuals who are likely to have inappropriately prescribed, unnecessary, or high-risk medication regimens, and may represent an opportunity to improve the functioning of older individuals that carries with it minimal risk and may have significant capacity to deliver improvements to quality of life (Rollason & Vogt, 2003; Trygstad et al., 2005).

### **Beneficial Effects of Polypharmacy of Cardiovascular Medication for Depression**

There are many potential mechanisms to explain the observed beneficial polypharmacy relationship, in which individuals taking more cardiovascular medications appear to be less depressed. Cardiovascular medication might be associated with the prevention of white matter pathology, or may possibly aid compensatory mechanisms such as increased cerebral blood flow and perfusion. At least one study has demonstrated improvements in frontal white matter functioning, as a result of successful treatment of

depression in older individuals (in that case, through electro-convulsive therapy), suggesting that improvements in white matter functioning may be an important pathway to improvements in depressive mood in late life (Nobuhara et al., 2004).

On the other hand, it is also quite possible that the beneficial polypharmacy associated with cardiovascular medications observed in the present study could be explained through improvements in physical health by virtue of successful medical management of cardiovascular disease. If it is the case that depression in cardiovascular disease is not a specific neurological effect of the disease process, but is rather a consequence of physical health impairment, then this depressive effect should be specific to a level of physical health impairment, and not to a disease category. The present study did not adequately assess physical health impairment as a potential mediator of drug effects, although this may well be a fruitful area for future research. Furthermore, successful treatments should improve depressive symptoms to the extent that they are successful in treating the underlying disease.

Supporting this viewpoint is research that has demonstrated that depression in individuals with organ failure requiring transplantation *was not* associated with the site of failure (when comparing individuals with heart, lung, and kidney failure), but *was* associated with the level of pain experienced (Forzberg et al., 1999). It is important to note, however, that this research was not performed on older individuals, in whom the associations among cardiovascular disease, white matter pathology, and depression, is believed to exist. Another study indicated that individuals whose heart failure was managed either by transplantation or by medication indicated that medication produced both better improvements in physical health and a substantial decrement in depressive

symptoms (Evangelista et al., 2005). However, that study was not able to demonstrate whether physical health management was a mediator of reduced depression in the medication group. Indeed, it is difficult to isolate the success of treatment in managing physical health from other benefits that are presumed to occur simultaneously in individuals who respond to cardiovascular treatment, such as improved cerebrovascular functioning.

Regardless of the relative power of the above explanations for the beneficial role of cardiovascular polypharmacy on mood symptoms in this population, the facts that individuals who received more cardiovascular medications showed fewer symptoms of depression, and individuals who received fewer cardiovascular medications showed more symptoms of depression is striking. Is it possible that cardiovascular disease may continue to be under-treated in this population, and that at least some of those individuals not receiving this medication might benefit from more aggressive treatment? Some evidence looking purely at the issue of adequate diagnosis and treatment of cardiovascular conditions in this population, suggests that this might, indeed, continue to be the case, due to complicated clinical presentation, the non-specificity of symptoms, access to care, particularly among impoverished elders, and other issues (Fitzpatrick et al., 2004; Frasure-Smith et al., 1993; Rich, 2005). Complicating this issue is the fact that not all individuals who are prescribed treatments for these conditions have the financial ability to obtain all prescribed medications (Piette et al., 2004).

### **Study Limitations**

There are several limitations to this study. First, the sample was relatively small, and did not include frail or institutionalized elders. While the latter aspect makes this study more representative of effects on community-dwelling elders, it also leads to

selecting individuals who are likely to be relatively less depressed and suffering from less severe cardiovascular pathology. Conclusions about the process of decline within older individuals that leads from low base rates of depression in the community to elevated base rates in the institutional population are difficult to draw in the absence of data on participants from both settings. In addition, since the present analysis is not longitudinal, it is impossible to make causal inferences. It is not clear whether individuals who are less depressed are more likely to need or use medication for cardiovascular conditions, for instance, or whether individuals who use more cardiovascular medications are less likely to become depressed.

This study utilized a method of operationalizing subsyndromal depression that has been used with success in the extant literature – namely, using scores from a self-report depression instrument as continuous variables. It was nonetheless successful in finding significant effects relating relatively low levels of depression and medication levels. However, the exact relationship between this method and other methods of conceptualizing depression below the level warranting a formal diagnosis of Major Depressive Disorder, such as the research criteria proposed in the DSM-IV-TR for Minor Depressive Disorder, remains unclear. The differences in the way this phenomenon is defined in different research studies limit the ability of this body of literature, as a whole, to make broad statements about sub-clinical, subsyndromal, minor, or minimal depression. Each study, however, presents results that are potentially individually meaningful, within the context of the definition adopted by the respective researchers, as the present study also seeks to do.

Because of limitations in assessing existing physical health conditions, and the longitudinal relationships between diagnoses of these conditions and prescription of medications, the present study is limited in that an thorough assessment of each participant's overall physical health and multimorbidity was not possible, and there is no way to truly differentiate polypharmacy in the sense of aggressive treatment and polypharmacy in the sense of overmedication. While it is implied here that cardiovascular medication, with its beneficial impacts, represents the former, and not the latter, it is also a component of polypharmacy, as measured, and is likely to contain, itself, both types of polypharmacy.

The present study did not investigate the impacts of specific medicines in detail, another technique that has provided compelling insight into changes in functioning in older individuals. Several methods for doing this have been developed. One of these methods is the investigation of relative risk associated with individual drugs (Dhondt et al., 2002; Veehof et al., 2000). A second method is the consideration of lists of drugs, such as the Beers Criteria, that are considered contra-indicated for older individuals in the majority of cases, based on known anecdotal or empirical evidence of problems associated with these medications in late life (Aparasu & Mort, 2000; Klarin et al., 2005). These methods have strengths in their ability to identify specific mechanisms based on the actions of individual drugs. However, the present method provides a complementary line of evidence, in that large, significant effects of broad classes of medication suggest the possibility of more basic mechanisms than those observed in studies of specific drugs. Such mechanisms are not likely to rely on the site of action or chemistry of a specific, individual drug, and may operate in parallel to the previously observed effects.

Finally, because this study did not make use of brain imaging techniques, no conclusive statements can be made about the associations among polypharmacy, state changes in the brain, and depression.

### **Conclusion**

In spite of these limitations, the present research contributes to the body of literature surrounding depression in older individuals by emphasizing the importance of considering medication-based management of chronic health conditions, especially cardiovascular conditions, within an integrated framework alongside other explanatory variables in the creation and maintenance of depressive symptoms in older individuals. This adds to the large body of literature that has demonstrated that elderly individuals with a history of cardiovascular risk burden are more likely to become depressed, and that these individuals are then likely to have white matter pathology and are at increased risk for strokes and for mortality, as well as with research indicating that functional disability due to chronic health concerns increases the risk of depression in the elderly, and suggests further investigation of management of the overall medication burden, as well as preventative and aggressive treatment of cardiovascular conditions, as possible elements of an overall healthcare program for older individuals that may have the capacity to prevent or eliminate some cases of depression in this population.

## LIST OF REFERENCES

- Alexopoulos, G. S. (1990). Clinical and Biological Findings in Late Onset Depression. *American Press Review of Psychiatry*, 9, 249-262.
- Aparasu, R. R. & Mort, J. R. (2000). Inappropriate Prescribing for the Elderly: Beers Criteria-Based Review. *The Annals of Pharmacotherapy*, 34, 338-346.
- Blazer, D. G. & Hybels, C. F. (2005). Origins of Depression in Later Life. *Psychological Medicine*, 35, 1241-1252.
- Blazer, D. G., Landerman, L. R., Hays, J. C., Simonsick, E. M., & Saunders, W. B. (1998). Symptoms of Depression Among Community-Dwelling Elderly African-American and White Older Adults. *Psychological Medicine*, 28, 1311-1320.
- Borowiak, E. & Kostka, T. (2004). Predictors of Quality of Life Among Older People Living at Home and in Institutions. *Aging – Clinical and Experimental Research*, 16, 212-220.
- Boyd, C. M., Darer, J., Boult, C., Fried, L. P., Boult, L., & Wu, A. W. (2005). Clinical Practice Guidelines and Quality of Care for Older Patients With Multiple Comorbid Diseases. *JAMA*, 294, 716-724.
- Bush, D. E., Ziegelstein, R. C., Tayback, M., Richter, D., Stevens, S., Zahalsky, H., & Fauerbach, J. A. (2001). Even Minimal Symptoms of Depression Increase Mortality Risk After Acute Myocardial Infarction. *The American Journal of Cardiology*, 88, 337-341.
- Caskie, G. I. L. & Willis, S. L. (2004). Congruence of Self-Reported Medications With Pharmacy Prescription Records in Low-Income Older Adults. *The Gerontologist*, 44, 176-185.
- Chopra, M. P., Zubritsky, C., Knott, K., Ten Have, T., Hadley T., Coyne, J. C., & Oslin, D. W. (2005). Importance of Subsyndromal Symptoms of Depression in Elderly Patients. *American Journal of Geriatric Psychiatry*, 13, 597-606.
- Christensen, D., Trystad, T., Sullivan, R., Garmise, J., & Wegner, S. E. (2004). A Pharmacy Management Intervention for Optimizing Drug Therapy for Nursing Home Patients. *The American Journal of Geriatric Pharmacotherapy*, 2, 248-256.
- Cleland, J. G., Baksh, A., & Louis, A. (2000). Polypharmacy (or Polytherapy) in the Treatment of Heart Failure. *Heart Failure Monitor*, 1, 8-13.

- Consedine, N. S. & Magai, C. (2003). Attachment and Emotional Experience in Later Life: The View From Attachment Theory. *Attachment & Human Development*, 5, 165-187.
- Dennerstein, L., Burrows, G. D., Hyman, G. J., & Sharpe, K. (1979). Hormone Therapy and Affect. *Maturitas*, 1:247-259.
- Dhondt, T. D. F., Beekman, A. T. F., Deeg, D. J. H., & van Tilburg, W. (2002). Iatrogenic Depression in the Elderly: Results From a Community-Based Study in the Netherlands. *Social Psychiatry and Psychiatric Epidemiology*, 37, 393-398.
- Evangelista, L. S., Dracup, K., Moser, D. K., Westlake, C., Erickson, V., Hamilton, M. A., & Fonarow, G. C. (2005). Two-Year Follow-Up of Quality of Life in Patients Referred for Heart Transplant. *Heart & Lung*, 34, 187-193.
- Field, T. S., Gurwitz, J. H., Avorn, J., McCormick, D., Jain, S., Eckler, M., Benser, M., & Bates, D. W. (2001). Risk Factors for Adverse Drug Events Among Nursing Home Residents. *Archives of Internal Medicine*, 161, 1629-1634.
- Fitzpatrick, A. L., Powe, N. R., Cooper, L. S., Ives, D. G., & Robbins, J. A. (2004). Barriers to Health Care Access Among the Elderly and Who Perceives Them. *American Journal of Public Health*, 94, 1788-1794.
- Flaherty, J. H., Perry, H. M., III, Lynchard, G. S., & Morkley, J. E. (2000). Polypharmacy and Hospitalization Among Older Home Care Patients. *Journal of Gerontology: Medical Sciences*, 55A, M554-M559.
- Forzberg, A., Lorenzon, U., Nilsson, F., & Bäckmana, L. (1999). Pain and Health Related Quality of Life after Heart, Kidney, and Liver Transplantation. *Clinical Transplantation*, 13, 453-460.
- Frasure-Smith, N., Lesperance, F., & Talajic, M. (1993). Depression Following Myocardial Infarction: Impact on 6 Month Survival. *JAMA*, 270, 1819-1825.
- Gibson, C. L., Gray, L. J., Murphy, S. P., & Bath, P. M. W. (2006). Estrogens and Experimental Ischemic Stroke: A Systematic Review. *Journal of Cerebral Blood Flow and Metabolism*, Advanced Online Publication, 1-11. Retrieved March 8, 2006, from <http://www.nature.com/jcbfm/journal/vaop/ncurrent/index.html>
- Gijsen, R., Hoeymans, N., Schellevis, F. G., Ruwaard, D., Satariano, W. A., & van den Bos, G. A. M. (2001). Causes and Consequences of Comorbidity: A Review. *Journal of Clinical Epidemiology*, 54, 661-674.
- Green, P. S. & Simpkins, J. W. (2000). Neuroprotective Effects of Estrogens: Potential Mechanisms of Action. *International Journal of Developmental Neuroscience*, 18, 347-358.

- Hogan, D. B. (1997). Revisiting the O Complex: Urinary Incontinence, Delirium and Polypharmacy in Elderly Patients. *Journal of the Canadian Medical Association*, 157, 1071-1077.
- Inzitari, D. (2003). Leukoaraiosis: An Independent Risk Factor for Stroke? *Stroke*, 34, 2067-2071.
- Johnson, J., Weissman, M. M., & Klerman, G. L. (1992). Service Utilization and Social Morbidity Associated with Depressive Symptoms in the Community. *JAMA*, 267, 1478-1483.
- Kingsbury, S. J., Yi, D., & Simpson, G. M. (2001). Rational and Irrational Polypharmacy. *Psychiatric Sciences*, 52, 1033-1035.
- Klarin, I., Wimo, A., & Fastbom, J. (2005). The Association of Inappropriate Drug Use with Hospitalisation and Mortality. *Drugs & Aging*, 22, 69-82.
- Krishnan, K. R. Hays, J. C., & Blazer, D. G. (1997). MRI-Defined Vascular Depression. *American Journal of Psychiatry*, 154, 497-501.
- Krishnan, M., Mast, B. T., Ficker, L. J., Lawhorne, L., & Lichtenberg, P. A. (2005). The Effects of Pre-Existing Depression on Cerebrovascular Health Outcomes in Geriatric Continuing Care. *Journal of Gerontology: Medical Sciences*, 60, 915-91.
- Lenze, E. J., Munin, M. C., Ferrell, R. E., Pollock, B. G., Skidmore, E., Lotrich, F., Rogers, J. C., Quear, T., Houck, P., & Reynolds, C. F., III. (2005). Association of the Serotonin Transporter Gene-Linked Polymorphic Region (5-HTTLPR) Genotype with Depression in Elderly Persons After Hip Fracture. *American Journal of Geriatric Psychiatry*, 13, 428-432.
- Lindeboom, M., Portrait, F., & van den Bergh, G. J. (2002). An Econometric Analysis of the Mental-Health Effects of Major Life Events in the Life of Older Individuals. *Econometrics and Health Economics*, 11, 505-520.
- Mamun, K., Lien, C. T. C., Goh-Tan, C. Y. E., & Ang, W. S. T. (2004). Polypharmacy and Inappropriate Medication Use in Singapore Nursing Homes. *Annals of the Academy of Medicine of Singapore*, 33, 49-52.
- Mast, B. T., Yochim, B., MacNeill, S. E., & Lichtenberg, P. A. (2004). Risk Factors for Geriatric Depression: The Importance of Executive Functioning Within the Vascular Depression Hypothesis. *Journal of Gerontology: Medical Sciences*, 59A, 1290-1294.
- McEvoy, G. K. (1996). *AHFS Drug Information*. Bethesda, MD: The American Society of Health-Systems Pharmacists.

- Mitnitski, A. B., Mogilner, A. J., MacKnight, C., Rockwood, K. (2002). The Mortality Rate as a Function of Accumulated Deficits in a Frailty Index. *Mechanisms of Ageing and Development*, 123, 1457-1460.
- Nobuhara, K., Okugawa, G., Minami, T., Takase, K., Yoshida, T., Yagyu, T., Tajika, A., Sugimoto, T., Tamagaki, C., Ikeda, K., Sawada, S., & Kinoshita, T. (2004). Effects of Electroconvulsive Therapy on Frontal White Matter in Late-Life Depression: A Diffusion Tensor Imaging Study. *Neuropsychobiology*, 50, 48-53.
- Oldehinkel, A. J., Ormel, J., Brilman, E. I., van den Berg, M. D. (2003). Psychosocial and Vascular Risk Factors of Depression in Later Life. *Journal of Affective Disorders*, 74, 237-246.
- O'Sullivan, C. (2004). The Psychosocial Determinants of Depression: A Lifespan Perspective. *The Journal of Nervous and Mental Disease*, 192, 585-594.
- Pantoni, L. & Garcia, J. H. (1997). Pathogenesis of Leukoaraiosis. *Stroke*, 28, 652-659.
- Piette, J. D., Heisler, M., Wagner, T. H. (2004). Cost-Related Medication Underuse Among Chronically Ill Adults: The Treatments People Forgo, How Often, and Who Is at Risk. *American Journal of Public Health*, 94, 1782-1787.
- Proctor, E. K., Morrow-Howell, N. L., Doré, P., Wentz, J., Rubin, E. H., Thompson, S., & Li, H. (2003). Comorbid Medical Conditions Among Depressed Elderly Patients Discharged Home After Acute Psychiatric Care. *American Journal of Geriatric Psychiatry*, 11, 329-338.
- Rich, M. W. (2005). Office Management of Heart Failure in the Elderly. *The American Journal of Medicine*, 118, 342-348.
- Roberts, R. E. (1980). Reliability of the CES-D Scale in Different Ethnic Contexts. *Psychiatry Research*, 2, 125-134.
- Rollason, V. & Vogt, N. (2003). Reduction of Polypharmacy in the Elderly: A Systematic Review of the Role of the Pharmacist. *Drugs & Aging*, 20, 817-832.
- Sloane, P. D., Zimmerman, S., Brown L. C., Ives, T. J., & Walsh, J. F. (2002). Inappropriate Medication Prescribing in Residential Care / Assisted Living Facilities. *JAGS*, 50, 1001-1011.
- Starr, J. M., McGurn, B., Whiteman, M., Pattie, A., Whalley, L. J., & Deary, I. J. (2004). Life Long Changes in Cognitive Ability Are Associated With Prescribed Medications in Old Age. *International Journal of Geriatric Psychiatry*, 19, 327-332.
- Taylor, W. D., McQuoid, D. R., & Krishnan, K. R. R. (2004). Medical Co-Morbidity in Late Life Depression. *International Journal of Geriatric Psychiatry*, 19, 935-943.

- Trygstad, T. K., Christensen, D., Garmise, J., Sullivan, R., & Wegner, S. E. (2005). Pharmacist Response to Alerts Generated From Medicaid Pharmacy Claims in a Long-Term Care Setting: Results From the North Carolina Polypharmacy Initiative. *Journal of Managed Care Pharmacy*, 11, 575-583.
- VanItallie, T. B. (2005). Subsyndromal Depression in the Elderly: Underdiagnosed and Undertreated. *Metabolism Clinical and Experimental*, 54, S39-S44.
- Veehof, L. J. G., Stewart, R. E., Haaijer-Ruskamp, F. M., & Mayboom-de Jong, B. (2000). The Development of Polypharmacy. A Longitudinal Study. *Family Practice*, 17, 261-267.
- Wallace, J. & O'Hara, M. W. (1992). Increases in Depressive Symptomatology in the Rural Elderly: Results From a Cross-Sectional and Longitudinal Study. *Journal of Abnormal Psychology*, 3, 398-404.
- Weiner, D. K., Hanlon, J. T., & Studenski, S. A. (1998). Effects of Central Nervous System Polypharmacy on Falls Liability in Community-Dwelling Elderly. *Gerontology*, 44, 217-221.
- Weissman, M. M., Sholomskas, D., Pottenger, M., Prusoff, B. A., & Locke, B. Z. (1977). Addressing Depressive Symptoms in Five Psychiatric Populations: A Validation Study. *American Journal of Epidemiology*, 106, 203-212.
- Whang, W., Albert, C. M., Sears, S. F., Lampert, R., Conti, J. B., Wang, P. J., Singh, J. P., Ruskin, J. N., Muller, J. E., & Mittleman, M. A. (2005). Depression as a Predictor for Appropriate Shocks Among Patients With Implantable Cardioverter-Defibrillators. *Journal of the American College of Cardiology*, 45, 1090-1095.
- Wilhelm, K., Mitchell, P. B., Niven, H., Finch, A., Wedgwood, L., Scimone, A., Blair, I. P., Parker, G., & Schofield, P. R. (2006). Life Events, First Depression Onset, and the Serotonin Transporter Gene. *British Journal of Psychiatry*, 188, 210-215.
- Ziegelstein, R. C. (2001). Depression After Myocardial Infarction. *Cardiology in Review*, 9, 45-51.

## BIOGRAPHICAL SKETCH

Mohan Krishnan graduated from the University of Michigan with a Bachelor of Science in engineering physics, in 1997, and a Master of Science in nuclear engineering and radiological sciences, in 1999. He then spent approximately 5 years working in various engineering and business roles within the automotive industry. During this time, he pursued coursework in psychology at Wayne State University, and participated in research studying the relationship between cardiovascular disease and depression in the elderly at the Wayne State University Institute of Gerontology. Currently, Mr. Krishnan is working toward a doctorate in clinical and health psychology, with a specialization in clinical neuropsychology, at the University of Florida.