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The Association between Untreated Depressive Symptoms and Polypharmacy in the Elderly in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study

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The Association between Untreated Depressive Symptoms and Polypharmacy in the Elderly in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study

By

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ABSTRACT

The Association between Untreated Depressive Symptoms and Polypharmacy in the Elderly in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study

By Albert Ma

Background. There is growing interest in the consequences of polypharmacy, particularly in determining the level at which treatment or detection of traditionally normalized chronic conditions such as depression are excluded among the medication-intense elderly. The goal of this study was to determine the association between polypharmacy and untreated depression in a large sample of elderly U.S. adults.

Methods. We used cross-sectional data from 11,484 participants aged 65+ in the Reasons for Geographic and Racial Differences in Stroke study. Medication count was collected during an in-home interview and stratified into 0-4, 5-9, and 10+ groups. Untreated depression was defined as no indication of antidepressant use and a score of 4+ on the four-item questionnaire derived from the CESD scale. Data regarding sociodemographic factors and comorbidities were also collected.

Results. The median medication count (IQR) was 6(3,8) for all subjects. The prevalence of untreated depression was nearly twice that for African Americans (10.5%) compared to whites (5.6%), and women (9.9%) compared to men (5.1%). The prevalence of untreated depression increased consistently with increasing polypharmacy strata from a prevalence (95%CI) of 6.3 % (5.56, 7.04) for 0-4 medications and increasing to 7.7 %(6.98, 8.42) and 9.5% (8.27, 10.81) among participants with levels of 5-9 and $\geq$10 medications, respectively. After adjusting for demographics and comorbid conditions, the association between polypharmacy and untreated depression was significant for only the highest strata of polypharmacy [OR (95%CI) 1.12 (1.12,1.76)] compared to the lowest. The association between the middle strata and untreated depression was positive but non-significant [OR (95%CI): 1.17(0.98,1.40)].

Conclusion. Within a large sample of elderly adults, there was a significant and positive association between those taking 10 or more medications and untreated depression after adjusting for sociodemographic factors and comorbidities.

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BACKGROUND/LITERATURE REVIEW

Introduction

People aged 65 and older represent one of the most rapidly growing age groups in the United States, accounting for approximately 39.6 million adults in 2009 and expected to reach 72.1 million, or 19% of the population, by 2030[1]. Subsequently, individuals older than 65 years have become the most active consumers of health care around the world, due in large part to increased longevity. However, the increasing number of medications prescribed to the elderly and the complexity of their drug regimens needed to manage myriad health concerns are of increasing concern. The issue of polypharmacy in the elderly is particularly concerning because of the multiple comorbidities common in this population, and the subsequent risks associated with drug interactions or under-prescribing by physicians attempting to avoid such complications. Due to its common association with other chronic conditions and pervasive normalization by both patient and physicians, elderly depression is commonly undertreated or not addressed[2, 3]. Given the negative effects of depression on health behaviors such as adherence to medical treatment and increased mortality from associated illnesses, the issue of polypharmacy and untreated depression requires further investigation.

The purpose of this literature review is to provide a broad overview of polypharmacy in the elderly population; first reviewing the descriptive epidemiology, risk factors, and associations with comorbid conditions, adverse drug reactions, and outcomes. Elderly depression will subsequently be discussed, first its epidemiology then its current treatment options, with an emphasis on the potential barriers to proper therapy and management of symptoms. Finally, this review will reveal the need for increased

attention to the treatment of depression in the elderly within the context of other comorbid conditions and subsequent polypharmacy.

Polypharmacy in the elderly

While Americans are living longer, they are doing so with multiple comorbidities which require complex drug regimens. Those 65 years of age and older comprise 12% of the population, yet this group accounts for 33% of all prescribed medication and 40% of nonprescription medications[4, 5]. Given the multiple chronic medical conditions common in this population including: hypertension, arthritis, heart disease, cancer, and diabetes mellitus, multiple concurrent medications are often required for optimal management of all indicated symptoms[6]. A national survey of 2,590 non-institutionalized adults indicated that 90% of adults 65 years or older used at least 1 medication per week, more than half used five or more different medications per week, and 12% use 10 or more different medications per week[7]. Surveys of community-based elderly patients show similar results in which two to nine prescription medications on average are taken per day with a majority of residents sampled taking at least five medications and use of 10 or more medications "was not unusual"[8]. A cross sectional study of community-dwelling persons demonstrated that this increasing trend is most prominent in the very elderly (those aged greater than 85 years) [9]. These observations were consistent with results from a large European study of 2,707 elderly home care patients which found that 51% of patients took at least six medications per day with the greatest concentration in the oldest of the group[10].

While there is no general consensus on definition, polypharmacy is commonly defined as the ‘concurrent use of more than anywhere between four and 10 medications’[11]. Because this definition does not take into account the number of comorbid diseases that require such treatment, an alternative definition often used for polypharmacy is, “the use of more medications than are clinically indicated’[12]. This distinction often makes defining polypharmacy difficult given the lack of consistent cut points. Previous studies have used anywhere between two and nine medications to identify polypharmacy depending on the population sampled. In general, European studies tend to define polypharmacy in terms of number of medications taken, whereas studies conducted in the United States tend to define polypharmacy according to the clinical indication[5].

In general, there is no distinction between prescription and over the counter (OTC) therapies, which is an important consideration in evaluating polypharmacy and the types of medications that are being prescribed and subsequently consumed. In their widely cited Slone Survey, Kauffman *et al.* reported that the most commonly used prescription medications in noninstitutionalized males over 65 years of age were: aspirin, acetaminophen, dioxin, warfarin, and furosemide, representing the top five in descending rank. For their female counterparts, acetaminophen, aspirin, conjugated estrogens, levothyroxine sodium, and hydrochlorothiazide represented the top five most commonly used medications, respectively [7]. A subsequent cohort study of Medicare enrollees reinforced these results in which cardiovascular agents, antibiotics, diuretics, opioids, and antihyperlipidemics were the most frequently used classes of prescription medications. Pain medications, cold and cough medications, vitamins, analgesics, antacids, and

laxatives were found to be commonly used nonprescription agents [13]. In general, women tend to use more medications than men, with this gender difference replicated in several studies in both average number and percentage of each gender using medication.

To further complicate the assessment of polypharmacy, different studies may include therapies outside of traditional prescription and OTC medications. Complementary or alternative therapies often are not considered to be medications, and so may not always be disclosed to primary care providers or study coordinators. In the Slone Survey, Kauffman *et al.* reported that 47% to 59% of older patients took vitamin or mineral supplements (multivitamins, vitamins E and C particularly) in addition to their prescribed regimen and 11% to 14% took herbal supplements (such as ginseng, *Gingko biloba* extract). As demonstrated, the descriptive epidemiology of polypharmacy in the elderly largely depends on the definition used (cut off for polypharmacy, prescription or OTC), population sampled (noninstitutionalized vs. community dwelling, age, country), and methodology used to assess medication usage.

Risk Factors for Polypharmacy

As described by Hajjar *et al.* identified risk factors for polypharmacy can broadly be classified into three groups: health status, demographic, and access to health care. There have been a number of studies conducted to identify the most relevant medical conditions or pattern of conditions that pose the greatest risk for polypharmacy. However, while there is some overlap in these results, as with most studies involving polypharmacy, the conclusions depend largely on the population investigated. As one would expect, the number of chronic conditions is a strong positive predictor for

polypharmacy (OR=4.5 CI: 3.4-6.0) [14]. In addition to the number of drugs, there are certain types of drugs that pose elevated risks. A Swedish study conducted by Bjerrum *et al.* found polypharmacy to be strongly and positively associated with individuals treated for cardiovascular diseases (OR=4.5 CI: 3.9-5.2), anemia (OR=4.1 CI: 2.7-6.1) and respiratory diseases (OR=3.6 CI: 3.1-4.1) [15]. In general, other chronic conditions such as diabetes mellitus (OR=1.7 CI: 1.4-2.0), depression (OR=1.2 CI:1.1-1.5), and pain (OR=1.7 CI: 1.5-1.9) increase the risk of increased drug use, as does general "poor health" (as defined by a Chronic Disease Index, OR= 1.41 CI: 1.19-1.66) [14]. Demographic characteristics such as increased age (OR=1.03 CI: 1.01-1.05) and years of education (OR=1.04 CI: 1.00-1.08), have been found to be significant positive predictors of polypharmacy while white race and female gender have been shown to increase risk in some studies but not in others [9, 14, 16]. With respect to access to health care characteristics, supplemental insurance (i.e. Medicaid OR=1.53 CI: 1.1-2.1) and continuity of care (OR: 1.33 CI: 1.02-1.73) are significant predictors of drug use [14, 16]. Given the heterogeneous nature of prescribing mechanisms around the world, it is difficult to compare these results across countries. Emphasizing the role of the prescribing physician in the risk of polypharmacy, Jorgenson *et al.* found that those who visited a primary care physician five or more times per year increased the risk of using five or more medications by 15 times (OR=15.41 OR: 5.74-41.34) [17].

Adverse Drug Reactions

The increasing number of chronic conditions requiring treatment is often compounded by physiological changes that come with aging. As the human body ages,

changes occur in organ systems and body composition including: changes in fat distribution, lower serum albumin for protein binding, reduced oxidative metabolism in the liver, and reduced glomerular filtration in the kidneys. Changes in the lean body mass to fat ratio can affect drug distribution, especially those that are lipid soluble such as fentanyl transdermal patches [4, 18]. Decreased blood flow in the kidneys and liver leads to decreased filtration and excretion of drugs in the former and decreased metabolism of medications by the latter. Because most medications require some type of break down before the body can remove it, any failures in the corresponding organ systems pose a risk of drug toxicity either in volume or through reactions with other drugs.

These age related changes in pharmacokinetics and pharmacodynamics leave elderly patients particularly vulnerable to potential complications of polypharmacy including drug-drug interactions and adverse drug reactions (ADR). An ADR as defined by the World Health Organization, is a "reaction that is noxious and unintended, and which occurs at dosages normally used in humans for prophylaxis, diagnosis, or therapy"[19]. The risk of ADRs increases with increased number of drugs taken; increasing 13% with use of two medications, 58% for five medications, and up to 82% for seven or more medications[5]. Currently, these ADRs account for anywhere between 12-25% of all hospital admissions in those 65 and older, but this number rises to 30% in people aged over 75 years [5, 20, 21]. In long-term care facilities where polypharmacy is pervasive given structured and enforced medication schedules, the reported rates of ADR are as high as 67-74% [8]. In their study of Medicare enrollees Gurtwitz *et al.* found an overall ADR rate of 50.1 per 1000 person years, with a rate of preventable ADR of 13.8

per 1000 person years[13]. The most common types of ADRs in this population were those involving the gastrointestinal tract (i.e. nausea, vomiting, diarrhea, constipation) at 22.1%, and electrolyte/renal events (16.7%). However, these estimates of ADR rates are difficult to compare with other related studies which have reported ADR rates in terms of ADR per 100 hospital admissions [22]. Once again, the influence of disparate clinical settings, patient populations, and reporting mechanisms must be taken into consideration before interpreting and comparing polypharmacy studies.

The pattern for ADR risk factors closely tracks with those seen with polypharmacy (as discussed earlier). Specifically, the risk of ADRs is strongly associated with multiple comorbidities and with the use of specific types of drugs [20]. Cardiovascular drugs (26%), antibiotics/anti-infectives (14.7%), diuretics (13.3%), non-opioid analgesics (11.8%), anticoagulants (7.9%), hypoglycemics (6.8%), and steroids (5.3%) represented the most frequent prescription drug classes associated with ADRs in the study conducted by Gurwitz *et al* [13]. Other older psychotropic drugs such as long-acting benzodiazepines and phenothiazine derivatives which have narrow therapeutic indices, in addition to phenytoin and theophylline, have been associated with ADRs in the elderly[4].

Geriatric Syndromes

Aside from the risk of adverse drug reactions/events, the use of multiple medications has been associated with an increased risk of drug-induced symptoms that can produce “prescribing cascades”. These result from misinterpretation of adverse effects as separate medical problems, which often leads to the prescription of further

drugs and a number of conditions often seen in the elderly community, termed “geriatric syndromes”, including urinary incontinence, impairments in cognition and balance, and mortality[6]. Tricyclic antidepressants such as amitriptyline or diphenhydramine can lead to drug-induced constipation [4]. Other central nervous system-acting drugs such as benzodiazepines have been shown to increase the risk of urinary incontinence (OR=1.44 CI: 1.12-1.83)[23].

Several studies have examined the effect of multiple medication use on impaired balance and falls. A study by Agostini *et al.* examined the relationship between cumulative medication and the risk of impaired balance in 885 community-dwelling residents aged 72 and older. There was an increased risk of 72% (OR=1.72 CI: 1.09-2.71) and 80% (OR=1.80 CI: 1.02-3.19) for impaired balance in those taking three to four or more medications, respectively. Taking angiotensin-converting enzyme inhibitors were also associated with increased risk of impaired balance (OR=1.3 CI: 1.1-3.0) [24]. Supporting previously reported effects of central nervous system activating medication, Weiner *et al.* found that among a community of male veterans aged 70 and older, taking two or more CNS active drugs (benzodiazepines, sedative/hypnotics, antidepressants, antipsychotics) increased the risk of falls by 2.37 (OR=2.37 CI: 1.14-4.94)[25].

Overall, the effects of polypharmacy alone on elderly morbidity and mortality have not been extensively studied, with the majority of data assessing inappropriate drug use rather than multiple drug use. However, as previously discussed, the risk of ADR increases with the number of prescriptions taken, and so these data may be used to infer possible relationships between polypharmacy and morbidity/mortality. In a cohort study

of 3,234 elderly participants, Hanlon *et al.* found a statistically significant association between inappropriate drug use and a decline in basic self-care among those with potential drug-drug or drug-disease conflicts (OR=2.04 CI: 1.32-3.16)[26]. Similarly, in a prospective study of community-dwelling women aged 65 year or older, Magaziner *et al.* found that polypharmacy was associated with declines in the ability to perform activities of daily living (ADL) and instrumental activities of daily living (IADL) even after controlling for covariates such as age, education, baseline functional status, and multiple comorbidities[27]. While Hanlon *et al.* did not find a significant association between inappropriate drug use and mortality, Espino *et al.* found that the risk of mortality increased by 51% (OR=1.51 CI: 1.28-1.80) among those who took more than four medications when compared to those taking four or less, which remained statistically significant after adjustments (OR=1.27 CI: 1.04-1.56)[28].

Adherence

An added yet equally important consideration in the effects of polypharmacy is that it creates complex medication regimens that make non-adherence a pervasive issue facing the elderly and their prescribing physicians. Hajjar *et al.* estimated the prevalence of non-adherence at an average of 50% in the elderly[20]. Others including Barat *et al.* have demonstrated a correlation between an increased number of prescriptions indicated per day and deviation from a given regimen (r=0.25, p=0.01). Moreover, there was a statistically significant positive association between non-adherence and the use of three or more drugs (OR=2.5 CI: 1.5-4.1)[29].

Undertreatment

Further complicating the issue of proper treatment regimens in the elderly, the undertreatment or- "nonprescription of an indicated drug without good reason" as defined by Holbeach- is paradoxically associated with polypharmacy. A study conducted by Kuljpers *et al.* showed that the probability of underprescription increased significantly with the number of medicines, whereby 43% of patients who used five or more medicines were undertreated[30]. These results support a previous study by Steinman *et al.* that estimated the underuse of medication in 64% of elderly outpatients sampled[31]. This body of literature suggests that primary care physicians that serve elderly patients are unwilling to prescribe additional pharmaceuticals to those with polypharmacy out of fear of ADRs, risk of interactions, and decreased adherence with increasing prescription count. This so-called "treatment-risk paradox" or "risk-treatment mismatch" indicates that patients at greatest risk for complications due to their comorbid conditions and therapeutic regimen are the least likely to receive the recommended pharmacological treatment for all indications. Cardiovascular diseases, hyperlipidemia, osteoporosis, chronic obstructive pulmonary disease, depression, and cancer are the most frequently underprescribed conditions in the geriatric population[16]. However, knowledge about the factors that influence the underuse of medications for common chronic diseases of older people is lacking, and there is a lack of information regarding functional and psychological factors that influence the use of medication by physicians.

Depression in the elderly

As mentioned previously, a consequence of increased life expectancy for many elderly populations around the world is a subsequent increase in comorbid chronic diseases. Depression represents an important consideration for gerontologists because of

its increased prevalence with age and associated comorbidities that negatively impact quality of life and health behavior. Epidemiological studies conducted in the 1990s and 2000s have provided a wealth of literature on late-life depression in North America, complemented by more recent reports from other countries in Europe and Asia.

Depression Case Definition

There remains considerable disagreement over what constitutes clinically significant depression and its multiple subtypes. From major to minor depression, and depression without sadness, dysthymic disorder, psychotic depression, early and late onset, and depression associated with Alzheimer's disease, the different ways of dissecting the syndrome becomes invariably difficult. However, depression can be broadly divided into major and minor presentations which are most relevant to the elderly population and will be discussed here in the discussion of descriptive epidemiology, but referred to as the more general term "depression" hereinafter.

Epidemiology of Late-Life Depression

Approximately 1-4% of the general elderly population has major depression, diagnosed in the DSM-IV as the presence of five or more of the following symptoms: depressed mood, diminished interest, loss of pleasure in daily activities, dramatic weight fluctuation ($\pm$ 5% bodyweight change), insomnia or hypersomnia, reduced concentration, or recurrent thoughts of death or suicide[32]. In general, a greater percentage of women are affected than men at all ages in both incidence and prevalence, with no significant ethnic differences[33, 34]. Palsson *et al.* determined an incidence of depression in a

Swedish population at 12 per 1000 person–years in men and 30 per 1000 person-years in women between the ages of 70 and 85 (statistically significant gender difference p = 0.001). Incidence increased from 8.7 and 23.2 per 1000 person years between the ages of 70-79 to 27 and 52.8 per 1000 person-years between the ages of 79-85, for men and women, respectively. In the United States, the estimate of incidence for major depression is considerably lower at 0.15% in the elderly, based on a representative sample of individuals born between 1901-1902 and longitudinally followed in the North Carolina Epidemiologic Catchment Area Study (ECA) [35]. In terms of prevalence, Palsson *et al.* estimated lifetime prevalence of depression at 23% in men and 45% in women, more than doubling between the ages of 70 and 85 for men and women combined. However, lower prevalence rates have been consistently observed in other settings outside of the Nordic populations. Estimates for different communities in the United States have ranged anywhere between 1.4-4.4% in women and 0.4-2.7% in men depending on the scale, location, and specific age group of the population[34].

Minor or sub-threshold depression is defined as two to five symptoms of major depressive disorder lasting for at least two weeks. In general, the prevalence of minor depression is greater than that observed for major depression. ECA estimates for minor depression and dysthymia were 6% combined while higher rates were again seen in the Nordic populations, with an estimate of 12.9% in the Netherlands[36]. Overall, reports of clinically significant depressive symptoms ranges anywhere between 8-16%.

As demonstrated, the distribution of late-life depression often depends on the population of elderly subjects, a pattern similar to those observed for polypharmacy as

previously discussed. In general, elderly subjects belonging to medical settings and the oldest old (those aged 85 year or greater) display higher rates than those in the community. The prevalence estimates for major depression among older adults hospitalized for medical services (both surgical and outpatient) is 10-12% with an additional 23% experiencing significant depressive symptoms[37]. In a large study of elderly patients residing in a long-term care (LTC) facility, 12.4% of the patients were indicated for major depression and 35% experienced significant depressive symptoms[38]. In another more recent study, Payne *et al.* found depression in 20% of patients admitted to a facility specializing in dementia and an incidence of major depression of 6.4% after one year of residence[39]. While a higher rate is often observed in the oldest of old (consistent observations of doubling in incidence and prevalence for those over 85 years of age), this elevated frequency is often explained by other factors associated with this aged population, including a higher proportion of women, greater physical disability and cognitive impairment, and lower socioeconomic status [32, 40]. The relationship between diagnosed depressive symptoms and age over 85 years disappears when these factors are controlled in subsequent analyses [41].

Outcomes of Late-Life Depression

Over long follow-up periods, major depression in the elderly has demonstrated a chronic remitting course in most clinical studies. A meta-analysis of available studies showed a 50% rate of chronicity in those alive after follow-up. In a longitudinal aging study conducted in Amsterdam, investigators followed 3,056 elderly people in the Netherlands for 10 years with regular administration of questionnaires and home

interviews (maximum 14 observations). In this sample, 23% of those with clinically significant depressive symptoms went into remission, 44% had an "unfavorable but fluctuating course" (remission and recurrence then chronic intermittent course), and 32% had a severe chronic course (no remission). Moreover, 35% of the patients suffering from major depression and 52% of the dysthymics experienced a "chronic course"[2]. However, in a sample of 239 elderly depressed outpatients, those who did not demonstrate significant comorbid conditions or dementia and who were properly treated exhibited a much more favorable outcome with over 80% recovering and remaining well throughout the follow-up period, in contrast to those peers who lacked social support and had poorer self-rated health who had a longer period to remission (HR=0.62 CI:0.39-0.97, HR= 0.55 CI: 0.37-0.83) [42]. In addition to highlighting the importance of interventions, these findings also emphasize the role that comorbid conditions play in the morbidity/mortality of elderly patients.

The association between depression and functional deficits has been reinforced over time through several longitudinal studies, demonstrating the effect on physical disability. In a longitudinal study of 6,247 elderly adults, Penninx *et al.* found that compared to their nondepressed counterparts, depressed subjects had a relative risk of 1.67 (CI: 1.44-1.95) and 1.73 (CI: 1.54-1.94) for incident disability in measures of activities of daily life (ADL) and mobility, respectively[43]. Even after adjusting for potential confounding characteristics including baseline chronic conditions and sociodemographic characteristics, the depressed subjects still demonstrated an increased risk for ADL and mobility disability (RR=1.39 CI: 1.18-1.63, RR=1.45 CI: 1.29-1.93, respectively). This study and subsequent longitudinal investigations have helped to dispel

the hypothesis that the association between depression and functional deficits is due to characteristics of depressed subjects (female gender, lower socioeconomic status, poorer health, excessive smoking and alcohol consumption). In addition to physical/mobile disabilities, severe depression has been established as a risk factor for Alzheimer's disease as well. In a longitudinal study comparing cognitively normal elderly volunteers and those with mild cognitive impairment (MCI), Li *et al.* found that early depressive symptoms in elderly patients with or without MCI may represent a risk factor for Alzheimer's or dementia[44].

As shown above, medical comorbidities such as depression and other functional impairments present in the elderly population adversely affect depression outcomes. In the same way, depression affects the outcome of those comorbidities as well, most observed with cardiovascular diseases. Depression is common in older patients recovering from myocardial infarction (MI) and other heart conditions, in those suffering from diabetes, hip fracture, and stroke[45]. In a cohort study by Romanelli *et al.*, older hospitalized patients with depression following a myocardial infarction were much more likely to die in the first four months after the MI (26.5% vs. 7.3% p=0.002)[46]. Additionally, Romanelli *et al.* found that older depressives were more likely to have had a prior MI (54.3% vs. 31.0% p=0.012) and an assortment of other cardiopulmonary anomalies. In a community dwelling of Mexican American elders, Black *et al.* found depression was additionally associated with arthritis (OR-1.42 CI: 1.17-1.72), urinary incontinence (OR=1.94 CI: 1.46-2.59), bowel incontinence (OR=2.28 CI: 1.15-4.55), kidney disease (OR-3.11 CI: 1.13-8.58), and ulcers (OR=2.56 CI: 1.23-5.29)[47]. The biologic mechanisms for these associations have not been clearly articulated, although

increased platelet activation is one potential theory that links depression and increased risk for morbidity/mortality with ischemic heart disease[48]. Additionally, frailty could be partially attributed to the decreased appetite frequently associated with depression, ultimately leading to a abnormal body mass index [45].

In addition to functional deficits, elderly depression has also been shown to be associated with all-cause mortality, although not consistently. These conflicting results may be in part explained by variations in sampling methods and sizes, study design, length of patient follow-up, varying definitions of depression (and its various subcomponents), and the degree to which confounders were accounted. In a systematic review of 57 published studies by Wulsin *et al*, 51% reported a positive association between depression and mortality, 23% reported no association, and 26% reported mixed findings. Schulz *et al* conducted a more recent systematic review of literature published between 1997-2001 and determined a relative risk for depression as a predictor of mortality between 1.2-4.0 with the majority between the 1.5-2.5 range [49]. Moreover, the association tended to be stronger in men than in women; an aspect that is largely supported throughout the literature, though could be due to study design factors that increase the effect seen in men because they are more likely to die within the follow up timeframe.

Because variables such as race and socioeconomic status are commonly used as control variables, there is little evidence supporting an association of depression and mortality stratified by characteristics. However, Shah, found that in LTC residents symptoms of depression were the only significant predictor of mortality, and within the

same study population, both depressive symptoms and self-esteem ratings were significant predictors of mortality[50]. Moreover, increased depressive symptoms have been hypothesized to depress immune system functioning, which can also raise the risk of mortality. In a sample of 171 adult patients of a long-term care facility, Yochim *et al.* found that increased depressive symptoms and lower performance on the DRS-2 (Dementia Rating Scale-2), were significant predictors of all-cause mortality (OR=1.04 CI: 1.00-1.09, OR=0.98 CI: 0.97-1.00)[51].

Pharmaceutical Treatment for Depression

Pharmaceuticals such as tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs) are the fundamentals of treatment for major and minor depression in older adults. Because all have been shown to be equally efficacious, and SSRIs are associated with fewer side effects, this class of medication has gradually replaced the others as the treatment of choice over the past 20 years[45, 52]. SSRIs such as fluoxetine, sertraline, paroxetine, citalopram, and fluvoxamine are the most commonly prescribed because of their improved tolerability and safety profile if taken in overdose, compared to previous generations of antidepressants such as MAOIs which had a history of potentially harmful pharmacodynamic drug interactions[45, 53]. The preferred anti-depressant for treating both major and minor depression is citalopram followed by sertaline and paroxtine.

The rise in antidepressant prescribing has been observed around the world. In a general practice research database of 189,851 patients, Moore *et al.* found a doubling of antidepressant prescribing in the study period, increasing from an average of 2.8

prescriptions per patient in 1993 to 5.6 in 2004. The authors attributed this rise mainly to small changes in the proportion of patients receiving long term treatment like those in the elderly population[54]. However, there have been relatively few drug utilization studies for older age groups, and information regarding prescribing levels for this population is heterogeneous with wide upper age groups and small sample sizes. Based on pharmacy data covering a population of ~470,000 people in Denmark from 1992-2004, Hansen *et al* found that among those 65 years and older, antidepressant use increased with age and did so during the last 3 years of life, whereby 33% of females and 25% of males indicated antidepressant use during their last 6 months of life[3]. As with other measurements of depression in the elderly, indications of antidepressant use may differ with age groups within the elderly, gender, physical health and other comorbid conditions.

Although depression is generally regarded as a treatable condition regardless of age using a combination of antidepressants and psychotherapy, most elderly persons with depression remain untreated[2, 3]. The explanations for these consistent observations can be categorized in terms of the antidepressants and conceptions of depression elderly that prevent them from receiving treatment. While second-generation antidepressants have a relatively low risk for pharmacodynamic interactions due to their more selective mechanism of action, there are clinically relevant side effects and interactions that have been attributed to this class of drugs. Elderly inpatients on SSRIs have a higher risk of developing hyponatremia (39% in one study), due to inappropriate secretion of antidireuctic hormone[45]. Because of their inhibitory effects on various Cytochrome P450 enzymes, the metabolism rate of certain agents (such as SSRIs) is decreased, increasing plasma drug concentrations and potentially enhancing pharmacologic

effects[53]. Other serious side effects reported with SSRIs include the risk of falls, the serotonin syndrome (lethargy, restlessness, renal failure, and possibly death), and gastrointestinal bleeding[45]. Indeed, there is growing evidence that a reason for older patients' aversion to antidepressants is due to fear of side effects associated with psychotropic medication. In a qualitative study conducted by Givens *et al*, the authors found four categories that comprised resistance to antidepressants: fear of dependence, fear that medication will disrupt natural sadness, prior experiences with previous drugs that had undesired sedative effects, and a reluctance to view depressive symptoms as a medical illness[55]. This last factor has been noted by other investigators who assert that elderly patients' feelings of distress are normalized by a conception that depression is a "natural part of the ageing process" that is common in the elderly who experience loss of loved ones or medical illness. This belief that depression is understandable and a function of broader social and contextual issues are often reinforced by primary care physicians who accept depression as a normal chronic disease or a normal response to difficult circumstances[56].

Summary

As discussed in this review, polypharmacy is pervasive in the 65 and older community, with a variety of risk factors such as health status, demographics, and access to health care that predispose certain populations to an array of (self) prescribed treatments for a variety of concurrent symptoms. However, this increased complexity of treatment regimen increases the risk for several complications, namely interactions with other comorbid illnesses or the medications used to treat them, in addition to other drug-induced symptoms that may lead to or exacerbate "geriatric syndromes".

A paradoxical yet plausible result of this balancing act by primary care physicians is the nonprescription of indicated drugs. Due to beliefs that normalize depression in the elderly, and fears of side effects associated with even the safest of antidepressants currently available, the treatment of depression has the potential to fall into this group of nonprescribed illnesses or "treatment-risk paradox". However, those with increased levels of depressive symptoms tend to have poorer self-care, which can lead to detrimental behaviors that interfere with health. This compounded with decreased adherence observed with increasing levels of polypharmacy, pose a real threat to the proper management of geriatric health, specifically psychiatric health, by the individual and provider alike. Therefore, the need exists for further investigation regarding the prevalence of untreated depression within the context of polypharmacy, which to date, has been scarcely addressed as a primary focus.

INTRODUCTION

People aged 65 and older represent one of the most rapidly growing age groups in the United States, representing 39.6 million adults in 2009 and increasing to 72.1 million, or 19% of the population, by 2030[1]. They have become the most active consumers of health care around the world, due in large part to increased longevity, accounting for 33% of all prescribed and 40% of OTC medications[4, 5].

The increasing number of medications prescribed to the elderly and complexity of drug regimens are of increasing importance. A national survey of 2,590 non-institutionalized adults indicated that on a weekly basis, 90% of those 65 years or older used at least 1 medication, more than 50% used five or more medications, and 12% used 10 or more[7]. Even higher levels of medication use have been observed among institutional patients[6]. Polypharmacy (the excess use of medications) in the elderly is concerning due to the prevalence of multiple comorbidities, compounded by age-related physiological changes affecting pharmacokinetics and pharmacodynamics [4, 12, 18]. The risk of adverse drug interactions accounts for 25% of all hospital admissions in this age group, leading to "prescribing cascades" in which reactions are misinterpreted as new symptoms and treated with more medication [5, 6, 20].

Under-prescribing by physicians is therefore not uncommon in this group due to the effects of polypharmacy on morbidity (impaired cognition, balance, and ability to perform daily activities) and mortality [24, 27, 28, 30]. This so-called "treatment-risk paradox" suggests that patients at greatest risk for complications are the least likely to receive recommended pharmacological treatment for all indications.

It is possible that depression falls under this "treatment-risk paradox" due to its common association with chronic conditions and normalization[57]. The perception of depression as a

function of broader contextual issues is often reinforced by physicians and further compounded by fears of antidepressant-associated side effects [2, 3, 56]. However, those with increased levels of depressive symptoms tend to also have poorer self-care, and combined with decreased adherence observed with polypharmacy, increase the risk for detrimental behaviors that interfere with proper management of geriatric health[20, 29].

It is uncertain to what extent the degree of polypharmacy affects treatment for elderly depression. While previous investigations have examined associations between polypharmacy and underuse of medications, literature has been restricted to therapies for other chronic conditions[58]. Moreover, the geriatric population has been underrepresented in these studies, and when included, often take place in the residential care or assisted-living settings. The purpose of this analysis is to determine the association between polypharmacy and untreated depressive symptoms among elderly adults in the general population.

METHODS

Study Design. This study was based on prescription data and demographic information collected as part of the REasons for Geographic and Racial Differences in Stroke (REGARDS). Further details regarding design and data collection have been previously described[59]. Briefly, the REGARDS study is a population-based cohort study of a representative sample of adults aged 45 years and older in the United States, designed to identify risk factors contributing to the excess stroke burden among African Americans in the Southeastern United States. The study cohort was recruited from a random probability sample with an oversampling of Stroke Belt states, African Americans, and men. Study enrollment began in February 2003 and recruitment concluded in October 2007.

Data. The REGARDS medication dataset consists of the medication lists from 28,029 of the 30,299 REGARDS cohort members. Data were obtained from each participant first through a telephone interview with a trained interviewer using a computer-assisted telephone interview (CATI). The CATI collected information regarding demographic factors, medical history, lifestyle, socioeconomic status, and cognitive and depression measures. The subsequent in-home visit collected anthropometric measurements (height, weight, waste circumference) as well as blood pressure, pulse, electrocardiogram and biological samples (serum and urine). Participants presented their current medications (prescriptions, OTC, vitamins, supplements, herbal remedies) used within two weeks prior to the visit, up to 20 of which were recorded on a standardized form by a visiting nurse. If medication could not be presented to the study nurse at the time of the recording, they were not recorded. Telephone follow-up was conducted every 6 months. Mortality was assessed every 6 months and cognitive function was assessed every 2 years. Only baseline data were collected for demographic factors and medication use.

Variables. The handwritten medication forms were transferred to a spreadsheet, which optically converted the lists into computer text using a handwriting recognition program. Each recorded medication was matched to a generic name for prescription and OTC medications, and subsequently assigned to a specific class using a scheme described by www.drugs.com. In order to explore dose-response effects, polypharmacy was classified according to medication count strata (0-4 medications, 5-9 medications, $\geq$ 10 medications) and included only prescription and OTC drugs. Though each medication may have had more than one biologically active ingredient, medication count was the unit of polypharmacy.

Depressive symptoms were evaluated through a series of four questions in the CATI requesting participants to recall the number of days during the past week for which he/she felt depressed, lonely, sad, or had crying spells. Responses were coded as one of: <1 day, 1-2 days, 3-4 days, 5-7 days, don't know, or refuse. The criteria for identifying potentially clinically significant depression were based on scoring by the Center for Epidemiologic Studies Depression Scale 4-item version (CESD-4). Each of 4 items was assigned one point value of 0, 1, 2, or 3 as follows: (less than 1 day=0, 1-2 days =1, 3-4 days = 2, 5-7 days = 3). Treatment for depressive symptoms was defined as the current usage of any kind of antidepressant at the time of evaluation. Exposure to untreated depressive symptoms was subsequently defined as those who were indicated to have potential clinical depressive symptoms based on CATI response (cumulative point sum of 4+) and no indication of antidepressant usage at time of evaluation. Individuals with CESD<3 and no indication of antidepressant use were categorized as not depressed.

Covariates for which information was collected include: date of birth, gender, and socio-demographic factors. These factors included: self-identified race, household income (income from all sources <$5000, $10000, $15000, $20000, or >$35000, $50000, $75000, $150,000), and

insurance status of any kind (including HMO or government plans). Prevalent coronary heart disease (CAD) was defined as self-reported myocardial infarction, bypass, angioplasty, stenting, or evidence of myocardial infarction via ECG. Dyslipidemia was defined as total cholesterol >240 or LDL$\geq$160 or HDL$\leq$ 40 or current use of medication. Diabetes was defined as self-reported use of medication, fasting glucose $\geq$126 mg/dL or non-fasting glucose $\geq$ 200 mg/dL. Hypertension was defined by an in-home blood pressure of SBP $\geq$ 140 mm Hg or DBP $\geq$ 90 mm Hg or self-reported treatment for hypertension. Stroke and kidney failure were defined by participant report of either at baseline.

Statistical Analysis. Descriptive statistics were used to summarize baseline medication, demographics, and comorbidities via univariate and bivariate analyses. χ^2 analyses, t-tests, and Mann-Whitney tests were conducted to examine differences in characteristics of subjects with untreated depression and no depression.

Logistic regression was conducted to determine the association between exposure to polypharmacy strata and untreated depression symptoms status. Crude and adjusted OR were calculated, comparing the odds for persons among the highest polypharmacy strata (5-9 meds and $\geq$10 meds) with the odds of persons in the lowest strata (0-4 meds) for untreated depression symptoms status (untreated depression vs. no depression). Potential confounders including: age, gender, race, socio-demographic factors (less than high school education, household income less than $20,000, no access to healthcare coverage) and presence of comorbid conditions were included in the fully adjusted model. For all statistical tests, α =0.05 determined statistical significance. Analyses were conducted using SAS 9.2 (Cary, NC).

RESULTS

Among the 30,879 eligible REGARDS participants, individuals were excluded if they were younger than 65 years of age (n=15,783), or if they were missing information on medication count (n=2,400) or CESD score (n=267). Only those with untreated depressive symptoms (n=866) and no depression (n=10,618) were included in this analysis. Among the remaining 11,484 (37.1%) subjects, the mean (SD) age was 72.7 (5.9) years with the majority (65.1%) in the 65-74 strata (Table 1). 4,546 (39.6%) were African Americans and 5,638 (49.1%) were males. The median medication count (IQR) was 6(3,8), and almost half (45.8%) of all subjects were taking between 5-9 medications. Most (98.9%) had access to healthcare and had at least a high school education (84.1%). Hypertension and dyslipidemia were the most prevalent comorbidities with 67.5% and 62.4% of all participants affected, respectively. Data regarding other socio-demographic characteristics for all subjects are presented in Table 1.

Compared to those with no depression, the untreated depression group had a smaller proportion of individuals with access to healthcare coverage (98% vs 99% p=0.0078), a greater proportion with incomes <$20,000 (39.3% vs 19.0% p<0.001), and twice the percentage of those with less than a high school education (31.3% vs 14.7% p<0.001) (Table 1). The prevalence of hypertension (73.7% vs 66.9%), stroke (12.5% vs 7.3%), and diabetes (31.3% vs 22.7%) were all significantly greater among the untreated depressed compared to the not depressed. The prevalence of untreated depression was nearly twice that for African Americans compared to whites (10.5% vs 5.6%), and women compared to men (9.9% vs 5.1%) (Table 2). The prevalence of untreated depression increased with age in a significant trend, from 6.3% among the youngest age group to 8.3% and 9.0% among those 75-84 and 85+, respectively.

The prevalence of untreated depression by polypharmacy distribution is presented in Figure 1. The proportion of those with untreated depression increased consistently in a

significant dose response trend with polypharmacy strata. Those taking 0-4 medications had a prevalence (95%CI) of untreated depression of 6.3 %(5.56, 7.04) which increased to 7.7 %(6.98, 8.42) and 9.5% (8.27, 10.81) among participants with polypharmacy levels of 5-9 and ≥10 medications, respectively.

The association between baseline characteristics and untreated depression is presented in Table 2. Men had lower odds of untreated depression when compared to women [OR (95%CI): 0.53(0.46, 0.62)]. Older age was associated with untreated depression, though only the middle strata (75-84 years) had significantly increased odds [OR (95%CI): 1.23(1.06, 1.44)] compared to the lowest age strata (65-74 years). African Americans had significantly greater odds of untreated depression when compared to whites [OR (95%CI): 1.8(1.59,2.11)]. Similarly, those with annual household incomes <$20,000 or less than high school education had more than double the odds of untreated depression with OR (95%CI) of 2.17(1.86,2.53) and 2.22(1.89,2.62), respectively, when controlled for age, race, and gender. Each comorbidity was significantly and positively associated with untreated depression except for dyslipidemia, with stroke [OR (95%CI): 1.79(1.44, 2.23)] and kidney failure [OR (95%CI): 1.60(1.05, 2.46)] demonstrating the largest magnitudes of effect, when adjusted for age, race, and gender.

The crude odds ratios (95%CI) for untreated depression according to polypharmacy strata were 1.23(1.05,1.45) and 1.55(1.28,1.89) for the 5-9 and ≥10 strata, respectively (Table 3). After adjusting for age, gender, and race, the associations remained positive and significant with adjusted odds ratios (95% CI) of 1.24(1.05,1.46) and 1.62(1.33,1.97) for the middle and highest polypharmacy strata, respectively. This increasing trend was statistically significant. Further adjustment for sociodemographic factors did not result in appreciable changes to the odds ratios (95%CI) for the middle 1.24(1.05, 1.46) or highest 1.61(1.32, 1.96) polypharmacy strata. In the final model controlling for all covariates, the association between polypharmacy and untreated

depression was no longer significant for the middle strata of polypharmacy [OR (95%CI): 1.17(0.98,1.40)]. The highest polypharmacy strata remained significantly and positively associated with untreated depression [OR (95%CI) 1.12 (1.12,1.76)].

DISCUSSION

There is growing interest in the effects of polypharmacy, particularly in determining the level at which treatment of traditionally normalized chronic conditions such as depression are excluded. Based on prior research among varying populations, we hypothesized that polypharmacy would be associated with untreated depression in a large sample of elderly community-dwelling U.S. adults. In this study we confirmed a significantly positive association between the highest strata of polypharmacy (10+ medications) and untreated depression, when controlled for sociodemographic factors and comorbidities. Moreover, the magnitude of this association was greater than that observed for the middle polypharmacy strata (5-9 medications), which demonstrated an increased though nonsignificant odds of untreated depression after multivariable adjustment.

The evidence linking medication count and untreated depression is fairly limited, and even more so in the general elderly population. In a cross-sectional study of institutionalized elderly individuals, Damian *et al*. found that the number of medications was a main determinant of untreated depression, with an 11% increase per additional medication [60]. We similarly found an increasing trend in prevalence of untreated depression with increasing polypharmacy. While the current analysis categorized medication count by strata, further analysis could be done to elucidate the association between untreated depression per unit of medication. Alternatively, polypharmacy and medication count may simply be a proxy for a collection of other factors that are associated with untreated depression. It is unclear whether it is the number of medications per se or the nature (comorbid indications) of these concurrent medications (or a combination of both) that contributes to the increased odds of untreated depression observed. Based on the results of several epidemiological studies, it has been speculated that the treatment of depression is at

least partially a function of the competing demands represented by different comorbid conditions, which may be indirectly represented by polypharmacy in this analysis..

In a cross-sectional patient survey, Rost *et al.* found that the attention paid to depression during a medical visit was more associated with the number of chronic physical comorbidities than with the severity of the patient's depressive symptoms[57]. An analysis of electronic health records data conducted by Gill *et al.* also found that individuals with multiple comorbid conditions were significantly less likely to be prescribed antidepressant medication than those with no comorbid conditions [aOR(95%CI): 0.58 (0.35,0.96)] [61]. Moreover, after controlling for age and sex, individuals with cardiovascular disease were less likely to be prescribed the full dosage of antidepressants [aOR(95%CI): 0.26(0.08-0.88)]. Because depression is more common among patients with a large comorbidity burden and is associated with increased risk of complications and mortality among those with diabetes, cancer, and cerebrovascular disease, the lack of depression treatment is unexpected given the improvements in outcomes for the previously described conditions[62-65]. This may be in part due to a culmination of other studies that suggested SSRIs and TCAs may actually increase risk of stroke among post-menopausal women or mortality after MI[66, 67]. The complexity of this evidence may be of great enough concern to primary care physicians so as to limit the prescribing of antidepressant medications to patients with a certain set of comorbidities[61]. Further studies using the REGARDS medication dataset may clarify if certain combinations of drug classifications are associated with untreated depression rather than the just the number of medications.

Limitations of this study's methodology include its cross-sectional evaluation precluding identification of potential causal relationships between polypharmacy and untreated depression. Medication count and comorbidities were only collected at the baseline in-home visit and limited to only medications presented at time of recording. While done without verification of medical

charts, this method of history ascertainment is consistent with previous investigations that require such information in non-institutionalized communities [14, 24, 28]. Because indication data were unavailable, antidepressant usage may not necessarily have indicated treatment for depression, as several antidepressants have been used to treat other conditions including neuropathic pain [68]. Moreover, while treatment only considered pharmacotherapy, psychotherapy is a commonly preferred alternative or complement particularly among the elderly with minor depression, and was not considered in the construction of the "untreated depression" categorization [32].

Factors affecting the evaluation of depressive symptoms may have also changed in the time following the interview. While the CESD has been found to have high sensitivity and specificity in identifying major depression when compared to the DSM-IV Structured Clinical Interview, it is unclear whether the adapted version used in this analysis maintained the validity of the full questionnaire, and to what degree minor depression was detected. Irwin *et al*. showed that the 10 question CESD achieves comparable reliability statistics as the original, with the optimal cutoff score of 4 points demonstrating high sensitivity, specificity, and positive predictive value for major depression only[69].

Despite these limitations, this analysis maintained several strengths. The findings were based on a large representative sample of the U.S. population, providing strong statistical power to detect small effect sizes. Previous studies measuring the association between polypharmacy and underuse of medication utilized relatively small homogenous groups of older adults (i.e. institutionalized veterans), limiting the external validity [70]. The random sampling of participants makes it unlikely that differences observed were due to disparities in participation. Data regarding confounders such as comorbid conditions and sociodemographic characteristics were collected and included in the analysis, important considering the associations previously described between comorbidity burden and depression.

These cross-sectional findings require longitudinal studies in which repeated observations monitor changes across time, providing information regarding the temporality of previously observed associations. Such follow-up data would more accurately characterize depression treatment beyond the initial baseline evaluation. Broadening the range of treatments for depression to include psychotherapy should also be considered. As some medications have been implicated in "substance induced depression", identifying patterns of pharmaceutical use most closely associated with the negative effects of polypharmacy could provide clinicians with information to better articulate the pharmaceutical risk factors for untreated depressive symptoms[32].

The clinical significance of the association between polypharmacy and untreated depression is evident from the increased odds of untreated depression observed among REGARDS participants taking the most medication. The issue of when it is appropriate to withhold treatment for an indicated condition among elderly individuals with a heavy comorbid or pharmaceutical burden is an important consideration, representing a fundamental clinical challenge for those caring for the elderly. More studies must be done to better articulate the effects of polypharmacy on the physical, as well as the psychological, well-being of patients so that prescribing physicians may be more cognizant of the potential risks inherent with polypharmacy.

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TABLES

Table 1. Demographic Characteristics by Treatment Status for Depression

Characteristic	All	Untreated Depressive Symptoms[1]	P[2]
Mean Age (SD)	72.7(5.9)	72.9(6.3)	0.159
Age			
65-74	7477 (65.1%)	532(61.5%)	0.0516
75-84	3553 (30.9%)	293(33.8%)	
85+	454 (4.0%)	41(4.7%)	
Gender			
Male	5638(49.1%)	287(33.1%)	<0.0001
Female	5846(50.9%)	579(66.9%)	
Race			
African American	4546(39.6%)	478(55.2%)	<0.0001
White	6938(60.4%)	388(44.8%)	
Median Medication Count (IQR)	6(3,8)	6(4,9)	<0.0001
Polypharmacy Strata			
0-4 pills	4180(36.4%)	265(30.6%)	<0.0001
5-9 pills	5259(45.8%)	406(46.9%)	
≥10 pills	2045(17.8%)	195(22.5%)	
Access to healthcare coverage	11353(98.9%)	847(98.0%)	0.0078
Annual household income			
<$20,000	2357(20.5%)	340(39.3%)	<0.0001
$20,000-$34,000	3304(28.8%)	242(27.9%)	
$35,000-$74,000	3194(27.8%)	114(13.2%)	
≥$75,000	1072(9.3)	27(3.1%)	
Refused	157(13.6%)	143(16.5%)	
Education			
Less than high school	1824(15.9%)	271(31.3%)	<0.0001
High school graduate	3051(26.6%)	280(32.4%)	
Some college	2843(24.8%)	180(20.8%)	
College graduate and above	3754(32.7%)	134(15.5%)	
Comorbidities			
Hypertension	7730(67.5%)	637(73.7%)	<0.0001
Diabetes	2579(23.3%)	258(31.3%)	<0.0001
Coronary Artery Disease	2695(23.9%)	235(27.9%)	0.0044
Stroke	876(7.7%)	108(12.5%)	<0.0001
Dyslipidemia	6921(62.4%)	498(59.9%)	0.1125
Kidney Failure	219(1.9%)	25(2.9%)	0.0286

[1] Percent of untreated depressive symptoms as measured by those with indicated depressive symptoms (≥4 CESD score) and no indicated usage of any antidepressants with characteristic.
[2] Statistically significant differences as measured by chi square analysis, t-test, or Wilcoxon-Mann-Whitney test

Table 2. Association between Participant Characteristics and Untreated Depressive Symptoms

Characteristic	Untreated Depressive Symptoms[1]	No Depression[2]	OR(95% CI)**
Age Strata N(%)			
65-74	532(7.1%)	6945(92.9%)	Ref
75-84	293(8.2%)	3260(91.8%)	1.23(1.06,1.44)
85+	41(9.0%)[3]	413(91.0%)[3]	1.37(0.98,1.91)
Gender N(%)			
Male	287(5.1%)	5351(94.9%)	0.53(0.46,0.62)
Female	579(9.9%)	5267(90.1%)	Ref
Race N(%)			
African American	478(10.5%)	4068(89.5%)	1.8(1.59,2.11)
White	388(5.6%)	6550(94.4%)	Ref
Polypharmacy Strata N(%)			
0-4	265(6.3%)	3915(93.7%)	Ref
5-9	406(7.7%)	4853(92.3%)	1.24(1.05,1.46)
≥10	195(9.5%)[3]	1850(90.5%)[3]	1.62(1.33,1.97)[3]
Access to healthcare coverage N(%)			
Yes	847(7.5%)	10506(92.5%)	Ref
No	17(13.8%)	106(86.2%)	1.66(0.98,2.81)
Annual income < $20,000 N(%)	340(14.4%)	2017(85.6%)	2.17(1.86,2.53)
Less than high school education N(%)	271(14.9%)	1553(85.1%)	2.22(1.89,2.62)
Comorbidities N(%)			
Hypertension	637(8.2%)	7093(91.8%)	1.18(1.01, 1.39)
Diabetes	258(10%)	2321(90.0%)	1.43(1.22, 1.68)
Coronary Artery Disease	235(8.7%)	2460(91.3%)	1.51(1.28, 1.77)
Stroke	108(12.3%)	768(87.7%)	1.79(1.44, 2.23)
Dyslipidemia	498(7.2%)	6423(92.8%)	1.00(0.87, 1.16)
Kidney Failure	25(11.4%)	194(88.6%)	1.60(1.05, 2.46)

[1] Percent of characteristic with untreated depressive symptoms as measured by those with indicated depressive symptoms (≥4 CESD score) and no indicated usage of any antidepressants.
[2] Percent of characteristic without depression defined as those with no indicated depressive symptoms (<3 CESD score) and no indicated usage of any antidepressants.
[3]Significant for test of trend
** All OR (95% CI) adjusted for age, race, and gender

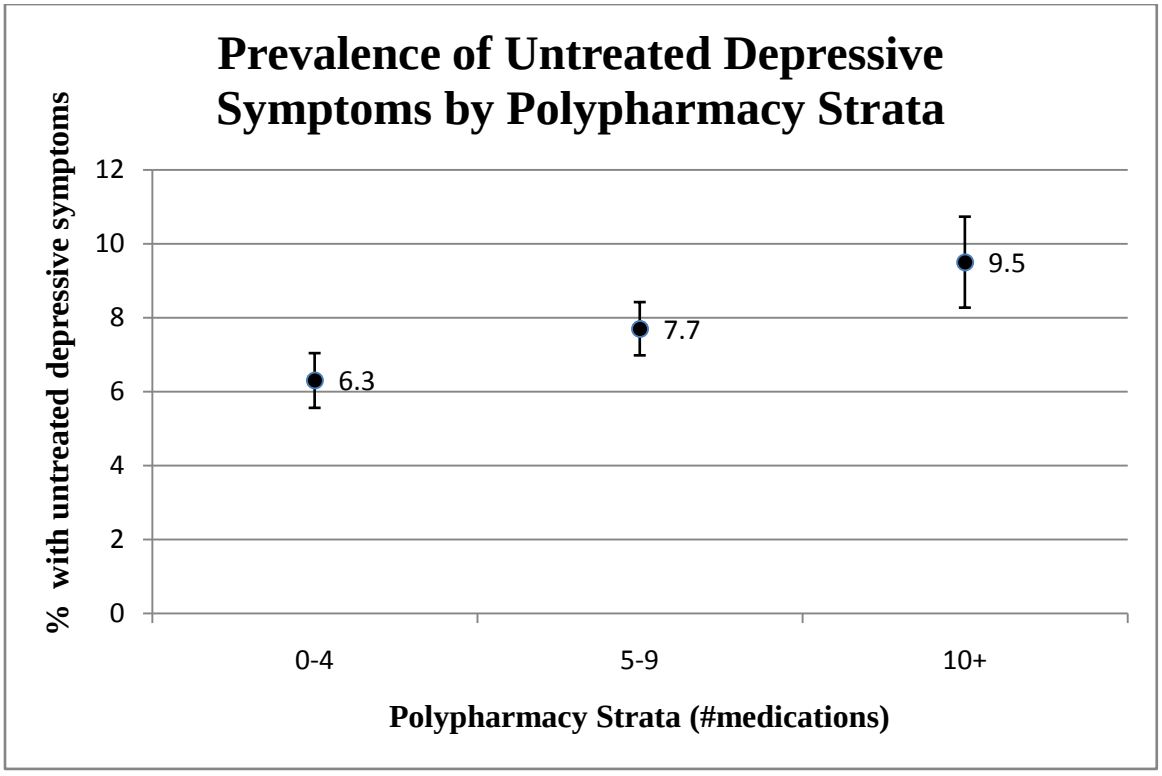
Table 3. Association between Polypharmacy Strata and Untreated Depression

	OR (95% CI) for Untreated Depression			
	Model 1	**Model 2**	**Model 3**	**Model 4**
Polypharmacy Strata	0-4 1.0 5-9 1.23(1.05,1.45) ≥10 1.55(1.28,1.89)	0-4 1.0 5-9 1.24(1.05,1.46) ≥10 1.62(1.33,1.97)	0-4 1.0 5-9 1.24(1.05,1.46) ≥10 1.61(1.32,1.96)	0-4 1.0 5-9 1.17(0.98,1.40) ≥10 1.41(1.12,1.76)
Age		65-74 1.0 75-84 1.22(1.05,1.42) 85+ 1.35(0.97,1.89)	65-74 1.0 75-84 1.14(0.97, 1.32) 85+ 1.19(0.85,1.67)	65-74 1.0 75-84 1.11(0.94, 1.29) 85+ 1.16(0.81,1.67)
Male Gender		0.54(0.47,0.63)	0.59(0.51,0.69)	0.55(0.47,0.65)
Black Race		1.9(1.65,2.19)	1.45(1.24,1.68)	1.37(1.16,1.61)
Socio-demographics income<$20,000 No insurance <high school education			1.88(1.6,2.19) 1.47(0.86,2.50) 1.87(1.58,2.21)	1.79(1.51,2.12) 1.53(0.88,2.66) 1.77(1.48,2.12)
Comorbidities Hypertension Diabetes CAD Stroke Dyslipidemia Kidney Failure				1.12(0.94,1.34) 1.16(0.97,1.38) 1.27(1.06,1.52) 1.45(1.14,1.84) 0.89(0.76,1.04) 1.28(0.80,2.04)

Shaded cells represent covariates not included in the particular model

FIGURES

Figure 1. Prevalence of Untreated Depressive Symptoms by Polypharmacy Strata



APPENDICES

EMORY UNIVERSITY | Institutional Review Board

April 28, 2011

Albert Ma
Rollins School of Public Health
Emory University
Atlanta, GA 30322

RE: Determination: No IRB Review Required
49849 - Title: *The Association Between Untreated Depressive Symptoms and Polypharmacy in the Elderly*
PI: Albert Ma

Dear Mr. Ma:

Thank you for requesting a determination from our office about the above-referenced project. Based on our review of the materials you provided, we have determined that it does not require IRB review because it does not meet the definition(s) of "research" involving "human subjects" or the definition of "clinical investigation" as set forth in Emory policies and procedures and federal rules, if applicable. Specifically, in this project, you will use de-identified data from the REGARDS medication database to determine if the proportion of participants with untreated depressive symptoms differs among degree of polypharmacy. This data will be supplied by your faculty advisor, Dr. William McClellan. The data is part of a limited data set obtained from the University of Alabama – Birmingham under a data use agreement.

This determination could be affected by substantive changes in the study design, subject populations, or identifiability of data. If the project changes in any substantive way, please contact our office for clarification.

Thank you for consulting the IRB.

Sincerely,

Sarah K. Clark, MPH, CIP
Senior Research Protocol Analyst
This letter has been digitally signed