10-19-2009

Use of Antidepressant Medications and the Subsequent Course of Depressive Symptoms among Older Adults

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A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

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2009

Abstract

Use of Antidepressant Medications and the Subsequent Course of Depressive Symptoms among Older Adults

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Antidepressant medications are commonly prescribed for older adults with depressive symptoms who may not have a major depressive disorder. Yet, the effect of antidepressants on depressive symptoms over time in this population is largely unknown.

We sought to determine whether the use of antidepressant medications is associated with a reduction in the severity of depressive symptoms over time.

Participants included 754 community-dwelling adults, aged 70+ years, who were followed at 18-month intervals for 90 months. Depressive symptoms were assessed using the 11-item CESD scale, with a higher score indicating worse depressive symptoms. A linear mixed effects model, adjusted for demographic features, number of chronic conditions, cognitive status, and physical frailty, was used to evaluate the effect of antidepressant use on change in depressive symptoms score over time. In addition, among persons with clinically significant depressive symptoms (i.e., CESD score >=20), we evaluated whether antidepressant use was associated with a transition to a non-depressed state (CESD score <20) using a Generalized Estimating Equations (GEE) model.

At baseline, participants taking an antidepressant (n=75) had higher mean CESD scores than those not taking an antidepressant (15.1$\pm$9.2 vs. 8.5$\pm$8.3; $p<0.001$) and were more likely to be female ($p<0.001$). Average unadjusted CESD change scores ranged from -3.4 to 1.7 and 0.4 to 1.5 among those taking, and not taking, an antidepressant, respectively (for the different 18-month intervals). Adjusted CESD scores worsened, on average, for participants taking an antidepressant as compared with those not taking an

antidepressant. These differences were statistically significant between baseline to 18 months (p=0.03), 36 to 54 months (p=0.02) and 72 to 90 months (p=0.01). The longitudinal findings indicated that CESD scores worsened by 2.2 points, on average, among participants taking an antidepressant as compared with those not taking an antidepressant, although this difference was not statistically significant (p=0.14). Among participants with clinically significant depressive symptoms, use of antidepressants was not associated with transitioning to a non-depressed state (OR=0.85, 95% CI 0.5-1.4).

Our findings raise concerns about the effectiveness of antidepressant medications, as prescribed in clinical practice. Additional research is needed to better understand the real world use and benefit of antidepressants among older adults.

Acknowledgements:

I am grateful to the following individuals: Dr. Lisa Barry for her amazing guidance through my master's project and thesis; I am especially grateful for our frequent conversations that clarified my thinking on my project and her positive outlook; Dr. Thomas Gill for his insight and for allowing me to gain a better appreciation for geriatric medicine; and Dr. Arthur Simen who provided a psychiatrist's perspective to my project. I would also like to acknowledge everyone at the Program on Aging, especially the statisticians and data managers who without their help this project could not come to a fruitful conclusion: Dr. Heather Allore, Dr. Peter van Ness, Linda Leo-Summers and Dr. Evelyn Gauhbauer.

This research was supported by NIA training grant (T32 AG1934).

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1. Background

1.1. Depression in Older Adults

Major depression, as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), affects 1-2% of community-dwelling older adults.[1] However, 6-18% of older adults experience clinically significant depressive symptoms that do not meet the DSM-IV criteria for major depression.[2-6] These clinically significant depressive symptoms are commonly referred to in the literature as elevated depressive symptoms or subthreshold depression, or subsyndromal depression.[7-11] A number of longitudinal studies have found that depressive symptoms are associated with worse health outcomes in older adults. For example, elevated depressive symptoms have been shown to be associated with increased mortality[12, 13] and comorbid conditions such as coronary heart disease[14] and type 2 diabetes.[15, 16] Depressive symptoms also have been found to be associated with decreased cognition, disability in activities of daily living, and decreased activity.[14, 15, 17-19] The risk for major depressive disorder and suicide also increases among older adults with elevated depressive symptoms.[11, 20] Furthermore, greater healthcare costs are accrued by older adults with elevated depressive symptoms.[21-23] Despite the public health significance of elevated depressive symptoms among older adults, however, this condition is still widely underrecognized and undertreated.

1.2. Classification of Depression

Depressive disorders are classified in many ways. Clinically relevant depressive disorders are defined by the DSM-IV and there are 3 main categories for depression 1) Major depression, 2) Dysthymia and finally 3) Minor depression. Major depression as defined by the DSM-IV as five (or more) of the following symptoms present during the

same 2-week period and represent a change from previous functioning; at least one of the symptoms is either depressed mood or anhedonia; 1) depressed mood, 2) anhedonia, 3) significant weight loss when not dieting or weight gain, 4) insomnia or hypersomnia nearly every day, 5) psychomotor agitation or retardation, 6) fatigue or loss of energy nearly every day, 7) feelings of worthlessness or excessive or inappropriate guilt, 8) decreased concentration, 9) recurrent thoughts of death. Dysthymia is characterized by an overwhelming yet chronic state of depression, exhibited by a depressed mood for most of the days, for more days than not, for at least 2 years. The symptoms are the same as those described for major depression. Elevated depressive symptoms is not a clinical diagnosis however it is made using screening tools for depression. The literature will occasionally refer to elevated depressive symptoms as depression or minor depression since the screening tools used are sensitive for detecting depression. However, without a DSM diagnosis we will refrain from assigning a clinical diagnosis to elevated depressive symptoms.

1.3. Underdiagnosis and Undertreatment of Depressive Symptoms

1.3.1. Underdiagnosis

Research suggests that major depression and elevated depressive symptoms in older adults are more likely to be diagnosed and treated by primary care physicians than by other specialists, such as psychiatrists.[24] It also has been indicated that older adults prefer to be treated by their primary care physician for problems related to mental health.[25] However, depression in older adults is frequently underdiagnosed and undertreated in the primary care setting.[26]

Patient-related factors may contribute to the underdiagnosis and undertreatment of depression in this population. Patients' fear of stigmatization of having depression, discomfort with medical treatment, belief that depression is part of normal aging, physical illness, and grief may delay or prevent older adults from seeking antidepressant treatment.[27, 28, 29-31] Givens et al.[32] conducted a qualitative study and found that older adults resisted antidepressant treatment due to four main reasons; 1) fear of addiction, 2) not viewing depression as a medical disease, 3) reluctance to prevent natural sadness, and 4) poor experience with prior medication. It is also possible that impairments in patients' vision, hearing or cognitive function might delay physicians' ability to recognize and diagnose depression because these impairments affect communication between the patient and physician.[33, 34] In addition, older adults are more likely to give socially desirable responses to physicians' inquiries about mood as compared with younger adults,[33, 35] thereby making it more difficult for physicians' to detect the presence of depressive symptoms.

Several physician factors also have been shown to contribute to the underdiagnosis and undertreatment of depression in older adults. Physicians may mistakenly think that persistent depressive symptoms are an acceptable response to aging-related illnesses or conditions.[36] For example, symptoms of depression are often mistaken for irreversible dementia.[37] Similarly, depression may be incorrectly considered as an inevitable response to loss of social support/socialization[38, 39] and to financial hardships that often accompany aging, rather than to a potentially treatable and reversible condition.[1] Lack of confidence when diagnosing and treating depression among older adults also may contribute to the underrecognition and undertreatment of depression. In

one study of 153 internists, only 55% and 35% felt confident diagnosing and treating depression, respectively, among their older adult patients.[40] Another potential problem is that physicians do not have enough time to establish rapport and to interview patients regarding nonmedical life issues, which could provide insight into distinguishing depression from other medical illnesses.[40]

Detection of depression can be accomplished through several formal screening tools available for use in older adults. These include the Center for Epidemiologic Study Depression Scale (CESD), Geriatric Depression Scale (GDS), or two simple questions about mood and anhedonia ("Over the past 2 weeks, have you felt down, depressed, or hopeless?" and "Over the past 2 weeks, have you felt little interest or pleasure in doing things?").[41-43] Evidence suggests that administration of a screening tool can improve recognition of depression in older persons. One study, in an emergency department setting, found that use of a screening tool such as the GDS identified 60% more cases of depression than physicians' assessments alone.[44] However, despite these prior findings and a recommendation by the U.S. Preventive Services Task Force (USPSTF) to screen adults for depression,[45] less than a third of physicians use a systematic screening device to evaluate depressive symptoms.[46] Consequently, there is ample opportunity to improve primary care physicians' recognition of depressive symptoms in older adults.

1.3.2. Undertreatment

Even when depressive symptoms are diagnosed in older adults, failure to treat depressive symptoms is common.[24] Luber et al. found that only one-third of the older outpatients who were diagnosed as depressed by their primary care providers received

antidepressant treatment.[30] In a study conducted in London, these investigators found that only 38% of patients mentioned their symptoms to their primary care physician; and of those found to have elevated depressive symptoms, only 14% were prescribed an antidepressant, while 24% were prescribed a hypnotic.[47] In a study by Callahan et al.[48], less than half of older adults identified as having depressive symptoms received antidepressant treatment.

1.4. Rates of Antidepressant Use Among Older Adults

Among older adults who are treated for depressive symptoms, antidepressants are the most common form of treatment. In a survey of 215 physicians, many physicians were uncertain about the benefits of psychotherapy for older persons. For example, only 57% thought that psychotherapy was as effective in older adults as it is in younger persons.[49] According to a cross-sectional study, only 1% of older adults have visited a psychotherapist.[50] A meta-analysis evaluating the efficacy of cognitive behavioral therapy (CBT) in older adults found that it was efficacious when compared to those waitlisted for psychotherapy.[51]

When antidepressants were first introduced, the first line therapies were Tricyclic Antidepressants (TCA's). However, side effects from these medications can be of concern in older adults because they can cause difficulties with memory and dizziness, and they increase the risk of falls.[52] Selective serotonin reuptake inhibitors (SSRI's) are now considered the first line therapy for depression and depressive symptoms in older adults as they have been shown to have fewer side effects and are better tolerated than TCAs.[52] In 1993, 9.6% of the antidepressants prescribed were SSRI's, while in 1997,

45.1% of the antidepressants prescribed were SSRI's, as determined through prescribing records for all adults.[53, 54]

Antidepressant prescribing and use has increased modestly in older adults during the last decade. The rate of antidepressant use in older adults, regardless of depression status, between the 1980's and the early 1990's ranged from 2.3% to 9.3%.[53, 55] In the late 1990's through the present, the rate of antidepressant use in older adults ranged from 8.1% to 11.5%.[53,55, 56] The increased use of antidepressants in the past decade is attributed to the availability of the SSRI's and increased knowledge and familiarity with these medications by prescribing physicians.[57] Nonetheless, even with the wider availability of SSRI's, older adults continue to be undertreated.[58]

1.5. Effectiveness of Antidepressants

1.5.1. Clinical Trials in Specialized Populations

Although antidepressant medication is the most common form of treatment for depression in older adults, relatively little is known about whether pharmacologic treatment improves depressive symptoms that do not meet DSM-IV criteria for depression, dysthymia or minor depression in this population. As will be discussed, most of what we know regarding the effectiveness of antidepressants in older adults comes from clinical trials, many of which have included mixed-age samples (i.e., participants < 65 years and ≥65 years), and specialized populations**,** such as patients who are institutionalized or being treated by a psychiatrist rather then a primary care provider, The results from such trials may not be generalizable to the population of depressed older adults who are commonly seen in clinical practice.

In 1997, a consensus statement was released regarding both pharmacological and non-pharmacological treatment of depression in late-life which stressed that there were effective treatments for depression and that aggressive approaches to diagnosis (i.e. routine screening followed by diagnostic testing for patients that have elevated depressive symptoms) and treatment (i.e. treatment for a long duration and medication at recommended doses) are warranted.[1] In 1999, a subsequent consensus statement was released that drew attention to the relative paucity of mental health care for the geriatric population and the need for increased research.[59] In preparation for the 2002 consensus statement on the treatment of depression in late-life, Salzman et al. evaluated clinical trials of antidepressant treatment in adults, aged 65 years or older. These investigators found that there has been an increase in the number of clinical trials evaluating the efficacy of antidepressants in older adults since 1994.[60] Between 1996-2001, 97 studies were conducted that evaluated antidepressant treatment in older adults; of these, 60 were comparative studies (i.e., efficacy studies) and 37 were trials that were inactive-placebo controlled trials.[60] These clinical trials generally found antidepressants to be effective, defined generally as a reduction in a depression score and/or remission of depression. However, the participants in these clinical trials were not representative of the general older adult population who most commonly receive these medications. Rather, the participants in these trials had major depression and/or dysthymia, diagnoses that are both defined by the DSM-IV; were primarily treated by specialists, such as psychiatrists, rather than primary care physicians; or represented specialized populations of older adults, such as in-patients, those in nursing homes or those with dementia.[60] Because these studies primarily evaluated the effect of antidepressant medication on depression

that met DSM-IV criteria, the effectiveness of antidepressants on depressive symptoms that do not meet the DSM-IV threshold remains unclear.

A landmark study, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D), evaluated a system that would optimize the delivery of antidepressant medication to outpatients in both a primary care setting as well as a psychiatric setting.[61, 62] The goals of the study were to demonstrate that proper delivery of antidepressant medication for depression in the "real-world" can be as nearly as effective as in clinical trials.[63] STAR*D was conducted in adults ≥55 years and operationalized remission as a score ≤5 on the Quick inventory of depressive symptomology-self rate score and improvement in mood was also measured by change in the Hamilton Depression Rating Scale HDRS-17 [64-66] [67] The study was designed to evaluate a 4-tiered algorithm for treating depression. Results from this study showed that the rate of remission was approximately 30% in all patients receiving Citalopram, which was the first line therapy. If the patient did not enter remission by 14-weeks, their medication was switched or augmented, subsequently resulting in remission in an additional 30% of the remaining subjects.[64] Unlike many clinical trials, this study included adults with significant comorbid medical and psychiatric problems, thus making the results applicable to a larger population.[65] One of the salient findings was that the majority of patients who were treated with an antidepressants for 14-weeks with Citalopram did not have remission of their depression.[66, 67] By augmenting or changing the antidepressant medications each 14-week step remission rates were about 33% after one step, 50% after two steps, 60% after three steps, and 70% after four steps.[61]

1.5.2. Clinical Trials in Primary Care

There are very few clinical trials examining antidepressant treatment in older community-dwelling adults who are treated by their primary care physicians; yet, this group comprises the majority of older adults who are prescribed antidepressants. A systematic review in 2001 by Freudenstein et al.[68] identified only seven high quality randomized controlled studies that evaluated the effectiveness of pharmacologic treatment of depression in a primary care setting and included older adults from a general, non-specialized population.[68] Studies by Ekselius et al. and Patris et al. compared two antidepressants, Citalopram vs. Sertraline and Citalopram vs. Fluoxetine, respectively, in older adults with major depression in the primary care setting.[69, 70] Both studies showed a reduction in the severity of depressive symptoms in each treatment group as ascertained by the Montgomery-Asberg Depression Rating Scale, with no difference between the antidepressant agents.[69, 70] None of the studies in this systematic review addressed the effectiveness of antidepressant treatment in older adults with depressive symptoms not meeting DSM-IV criteria.

In addition to the studies identified by this systematic review, we identified a randomized controlled trial that evaluated the effectiveness of antidepressant treatment in older adults without major depression in a primary care setting. Participants were classified as depressed if they met DSM-IV criteria for dysthymia or had met modified DSM-IV criteria for minor depression, meaning that they were required to have 4 weeks of 2 to 3 symptoms rather than 2 weeks of 2 to 4 symptoms usually required for the diagnosis. In this randomized controlled trial, participants treated with the antidepressant medication Paroxetine showed moderate improvement of dysthymia and minor

depression, as determined by comparing the mean reduction in the 20-item Hopkins Symptom Checklist Scale in the treatment group with those who received placebo.[71]

A very recent meta-analysis[72], which was not restricted to older adults, compared the efficacy and acceptability of 12 major antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, and venlafaxine) among persons with major depression. Escitalopram, mirtazapine, sertraline, and venlafaxine were significantly more efficacious than the other antidepressants. Efficacy was defined as a reduction of at least 50% from the baseline score on the Hamilton depression rating scale (HDRS) or Montgomery–Asberg depression rating scale (MADRS), or who scored much improved or very much improved on the clinical global impression (CGI) at 8 weeks. Among the four antidepressants that were found to be efficacious, sertraline and escitalopram were the best tolerated.

1.5.3. Observational Studies in Primary Care

To the best of our knowledge, no studies have evaluated the efficacy or effectiveness of antidepressants in older adults seen in primary care whose depressive symptoms do not meet a DSM-IV threshold for depression, dysthymia or minor depression. In the Personnes Agees Quid (PAQUID)[73] study, a large representative cohort of older community-dwelling older adults age $\geq$ 65 in southwest France, the researchers evaluated antidepressant use and depressive symptoms between 1988-1999.[73] Whereas this study found that the prevalence of participants with depressive symptoms decreased during the span of the study, while antidepressant use increased during the

same time period it did not determine whether antidepressants were associated with a reduction in depressive symptoms.

In a longitudinal study, Blazer et al. [74] also attempted to determine the association between antidepressant use and depressive symptoms. These investigators found no association between antidepressant use and the overall burden of depressive symptoms. However, the study was not designed to determine the effectiveness of antidepressant medications, but did show that the CESD Scale scores were not significantly associated with antidepressant use.

The effectiveness of antidepressants in a more natural or "real world setting" is uncertain. The few available "real world" studies (i.e. studies that recruit participants from the community and have more lax inclusion/exclusion criteria) have shown that nearly 80% of older adults who are treated for their depression by their primary care physician fail to improve or relapse back into depression by 6 months to 2 years.[75-77]

1.6. Questioning the Current Research on Antidepressant Efficacy

Much of the published research on antidepressant efficacy in adults, not limited to those age 65 and older, have reported modest benefits. However, two recent meta-analyses, which have evaluated the efficacy of antidepressants by combining published and unpublished reports, have demonstrated that the efficacy of antidepressants is likely overstated due to publication bias.[78] Furthermore, a recent report by Turner et al.[78], comparing data from the Food and Drug Administration (FDA) to publications related to antidepressant drug efficacy, found widespread discrepancies. Specifically, Turner et al. [78] identified 74 FDA registered studies that involved tests of antidepressant efficacy. They

found that 31% of the studies were not published, involving 3449 study participants. Of the 74 registered FDA studies with positive findings, 37 out of the 38 were published. While out of 36 studies with negative findings, 22 were not published, 11 were published in a misleading way that made them appear positive, and 3 were published in a way that accurately reflected the negative results. Published studies suggested 94% of studies were positive, whereas the FDA records showed that 51% were positive.

In a recent meta-analysis by Kirsch et al.[79], when data from the FDA were combined with those from published reports, the drug–placebo differences in antidepressant efficacy increased as a function of baseline severity, but the benefits were relatively small even for most severely depressed patients.[79]

1.7. Antidepressant Use and Transitions Between Depression States

Because depression is often a chronic condition with a remitting/relapsing course,[80, 81] preventing the next episode of depression is important. A meta-analysis identified studies that evaluated the prognosis of depression and elevated depressive symptoms in older adults (age >60). They identified 12 studies of the prognosis of depression in elderly community and primary care populations. The combined results of these studies indicated that 24 months after enrollment, 33% were well, 33% were depressed, and 21% had died.[77] In two years the prognosis of depression is poor in older adults.

The remitting/relapsing nature of depression may be evaluated by taking into consideration transitions between a depressed state and not depressed state. Recent evidence from the PEP Study has indicated that transitions into and out of depression in

older persons occur frequently over a 72-month period, a longer timeframe than has previously been evaluated.[82] Of the 269 participants (35.7%) who were depressed at some point during the 72 months of follow-up, 48 (17.8%), 30 (11.2%), 17 (6.3%), and 12 (4.5%) were depressed during 2, 3, 4, and 5 consecutive time points, respectively.[82] Based on prior analysis of the PEP data not all participants who were depressed remained depressed and some participants who were not depressed transitioned to a depressed state. The study's primary aim was to determine if there were gender differences between those who transitioned into or out of depression. A transition from a depressed state to a non-depressed state may be considered to be remission or recovery from depression. Similarly, a transition from a non-depressed state to a depressed state may represent relapse.

In the current study, we sought to evaluate the association between treatment with antidepressant medications and changes in depressive symptoms over time in community-dwelling older adults, thereby improving the "real-world" understanding of how antidepressant medications impact depressive symptoms in this population.

2. Specific Aims

Aim #1

To characterize depression and antidepressant use among older adults over time.

Aim #2A

To test the hypothesis that the use of antidepressant medications is associated with a reduction in depressive symptoms in older adults over time.

Aim #2 B

To test the hypothesis that the likelihood of transitioning from a depressed state to a non-depressed state will be higher among those taking antidepressant medications as compared with those not taking antidepressant medications.

3. Methods

3.1. Study Population

The study sample included the 754 participants of the Precipitating Events Project (PEP), a prospective cohort study of nondisabled, community-living persons aged 70 years or older residing in New Haven County.[83] Enrollment occurred between March 1998 and October 1999, and participants were identified though a computerized listing of 3157 age-eligible members of a large health plan in New Haven, Connecticut. Potential participants were mailed a letter that briefly described the study and explained that they would be contacted by phone. During the phone interview, eligibility was assessed, and a home visit was scheduled among consenting eligible persons. During the home visit, eligibility was verified, informed consent was obtained, and a comprehensive baseline assessment was completed.[83]

PEP was designed to evaluate the effect of precipitating events (e.g., hospitalization) on subsequent disability in older persons. Members were eligible if they were community-living, English-speaking, and nondisabled (required no personal assistance) in four key activities of daily living: bathing, walking across a room, dressing, and transferring from a chair. Plan members were excluded based on three criteria: diagnosis of a terminal illness with a life expectancy less than 12 months, plans to move out of the New Haven area during the next 12 months, and significant cognitive impairment with no available proxy.[83] The participation rate was 75.2%. During the 7.5-year follow-up period between March 1998, and January 2007, 279 participants died after

a median of 54 months, and 32 dropped out of the study after a median of 27 months. The Human Investigation Committee at Yale University approved the study.

3.2. Data Collection

Face-to-face in-home assessments were completed at baseline and every 18 months for up to 90 months (i.e., up to 6 possible assessments) by highly trained research nurses using standard procedures. Each nurse was thoroughly trained and the interviews were guided by the use of an assessment booklet that included all scripts to be read to the participant followed by a prompt to the next question.

During the baseline assessment, data were collected on age, gender, race, and educational level. During the baseline and each subsequent face-to-face assessment, medical comorbidity was ascertained based on the presence of nine self-reported, physician-diagnosed chronic conditions, including hypertension, myocardial infarction, congestive heart failure, stroke, diabetes, hip fracture, arthritis, chronic lung disease, and cancer. Cognitive status was assessed during each assessment using the Folstein Mini-Mental State Exam (MMSE), with scores ranging from 0 (lowest) to 30 (highest).[84] Gait speed was assessed by asking the participants to walk back and forth over a 10-foot (3-m) course as quickly as possible. A timed score of greater than 10 seconds on the rapid gait test indicated that the participant was physically frail.[85] Deaths were identified and confirmed by review of local obituaries and/or an informant.

3.2.1. Independent Variable: Antidepressant Use

Use of antidepressant medications was ascertained directly by a one of the trained nurse researchers. Participants were asked to retrieve all of their medications and were reminded to check their purse and night table, etc. If a medication was not retrieved, the nurse asked to see the participant's medication list. If a list was unavailable, they were asked to recall medications taken in the last two weeks. The nurse wrote down the name of each of the medications on the data collection form and antidepressant medications were subsequently coded based on the American Hospital Formulary system (AHFS) code 28.16.04.

In the present study, antidepressants included the use of a Tricyclic antidepressant (TCA), Selective Serotonin Reuptake Inhibitors (SSRI), or Non-SSRI/Non-TCA. Trazodone was not considered an antidepressant because it is primarily prescribed as a sleep aid.[86] Similarly, Amitriptyline was not included as an antidepressant because it is most commonly prescribed in older persons as a sleep aid or for pain at lower doses; and data were not collected on medication dose or schedule.[87-90]

3.3. Primary Outcome Variable: Depression Change Score

Depressive symptoms were assessed during each of the six face-to-face assessments (i.e., baseline, and 18, 36, 54, and 72 and 90 months) using the 11-item Center for Epidemiological Studies-Depression scale (CESD).[42, 43] The CESD asks about symptoms that have occurred during the past week, such as "I did not feel like eating; my appetite was poor" or "I enjoyed life". Responses on each of the 11 items were scored 0 = rarely or never, 1 = some of the time, or 2 = much or most of the time and were subsequently summed to yield a total depressive symptoms score for each participant. Scores were transformed to be compatible with the 20-item CESD[91]; hence, total scores

ranged from 0 to 60, with higher scores indicating more depressive symptoms. Depressive symptoms data were complete for 100% of the participants at baseline and 95%, 93%, 91%, 90% and 95% of the non-decedents at 18, 36, 54, 72 and 90 months, respectively.

Change in depressive symptoms was determined for each 18-month interval by calculating the difference in the CESD Scores between the two relevant time-points (i.e. the baseline CESD score was subtracted from the 18-month CESD score.) A negative change score indicated an improvement in symptoms while a positive change score indicated a worsening of symptoms.

Table 1: CESD Depression Scale

nstruction to Participant:

I would now like to ask you a few questions are about how you have been feeling. For each of the following statements, please tell me how often you have been feeling that way <u>during the past week.</u>

		Rarely or never	Some of the time	Much or most of the time	REF	DK
1.	I felt that everything I did was an effort – How often have you been feeling this way?	1	2	3	7	8
2.	I did not feel like eating; my appetite was poor.	1	2	3	7	8
3.	My sleep was restless.	1	2	3	7	8
4.	I felt depressed.	1	2	3	7	8
5.	I was happy.	1	2	3	7	8
6.	I felt lonely.	1	2	3	7	8
7.	People were unfriendly.	1	2	3	7	8
8.	I enjoyed life.	1	2	3	7	8
9.	I felt sad.	1	2	3	7	8
10.	I felt that people disliked me.	1	2	3	7	8
11.	I could not get “going”.	1	2	3	7	8

3.4. Secondary Outcome Variable: Transitions into and out of Depressed/Not Depressed States

Participants with CESD scores ≥20 were considered to be depressed. This cut point has previously been shown to enhance the likelihood of detecting subsyndromal depression among community-living older persons.[92,93] Participants were classified as depressed, non-depressed, or dead at each time-point. Transitions for the purpose of this study was defined as passage from one state to another, also including the possibility that they remain in the same state. Participants subsequently could have 6 possible transitions from one time-point to the next: 1) depressed to not depressed; 2) depressed to depressed; 3) depressed to dead; 4) not depressed to depressed; 5) not depressed to not depressed; 6) not depressed to dead. While evaluating the association between antidepressant use and death was not a primary aim of the study, this transition needed to be included in order to account for the significant source of missing data. The missing data in longitudinal epidemiological studies on older adults is often death, and to assume they are missing at random would bias the results.

3.5. Statistical Analysis for Univariate and Bivariate Findings

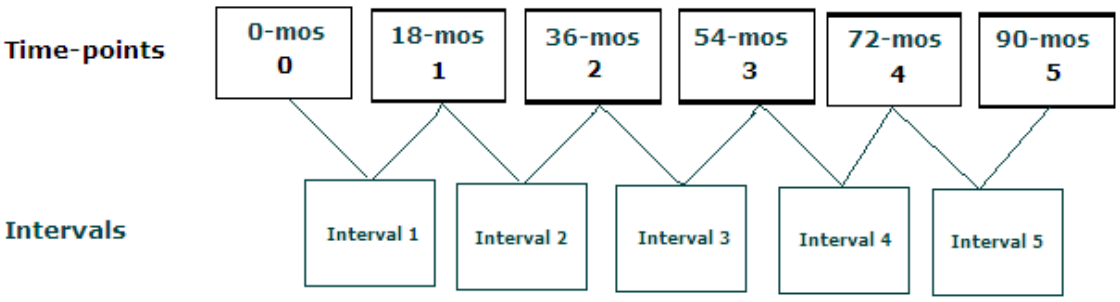
At each time-point, we determined the descriptive statistics f for the demographic (age, race, gender and education level) and the clinical covariates (number of chronic conditions, cognitive status score, physical frailty and depressive symptoms). We compared participant characteristics (demographic and clinical covariates) between those with and without depression, and those who were and were not treated with an antidepressant medication using χ^2 or *t* test statistics at each time-point.

3.6. Change Score Model

3.6.1. Statistical Analysis for Change Score Model

We compared the depression change score between those who were and were not treated with an antidepressant for each 18-month interval using general linear models. Intervals refer to two time-points that are combined. The descriptive data such as age, CESD score, MMSE, frailty and number of chronic conditions in each interval was from the earlier time-point. For example, the data in Interval 2 would contain the descriptive data would be from the 18-month interviews in addition to the change score and transition data that will be described in the following paragraphs. Using intervals, we can evaluate the association between antidepressant use at the beginning of each interval and subsequent change in depressive symptoms from the beginning to the end of the interval. The following figure illustrates how the time-points combined make up the intervals that will be discussed.

Figure 1 :Illustration of time-points versus intervals



Three models were run to evaluate the association between antidepressant use and change in depressive symptoms. The first model was unadjusted, the second was

adjusted for demographic features (age, race, gender and education), and the third was adjusted for demographic such as: age (continuous), race (white vs. other), educational level (continuous variable), and clinical covariates such as: number of chronic conditions (continuous variable), frailty (yes vs. no) and cognitive status (continuous score).

We evaluated the longitudinal association between antidepressant use and depression change score by using a repeated measures linear mixed model. The covariance structure was chosen by determining which model had the best fit by comparing the Akaike's information criterion (AIC). The AIC allows us to determine the goodness of fit of our estimated statistical model. The different model structures were ranked according to their AIC and the final covariance structure chosen was the Toeplitz model since it had the lowest AIC, thus providing the best fit.

3.7. Transition Models

3.7.1. Statistical Analysis for Transition Models

For each of the 18-month intervals, we calculated transition rates according to whether (or not) participants were taking an antidepressant medication for the six possible transitions, defined based on the three outcome states: non-depressed, depressed, and death. χ^2 or Fisher exact statistics were used to evaluate the bivariate associations between treatment and the six possible transitions for each time interval. To determine whether the observed transitions were clinically meaningful, we calculated the percentage of transitions that represented absolute changes in the CESD scores of 1 to 3 (small), 4 to 9 (moderate), 10 to 19 (large), and 20 or more (very large) points for each time interval.

We evaluated the association between antidepressant use and the likelihood of the 6 possible transitions over time using longitudinal methods that optimized statistical power. The first longitudinal model included participants who were not depressed at the beginning of any 18-month interval, with participants who were not depressed during the entire interval (i.e., at 2 consecutive 18-month time points) serving as the comparison group. Specifically, we ran generalized multinomial logit models for nominal outcomes that were estimated with a generalized estimating equation and used exchangeable correlation structures. The second longitudinal model included participants who were depressed at the beginning of any 18-month interval, with participants who were depressed during the entire interval serving as the comparison group.

The magnitude of association was determined by odds ratios, which were adjusted for age (continuous), race (white vs. other), educational level (continuous variable), number of chronic conditions (continuous variable), frailty (yes vs. no) and cognitive status (continuous score). Prior to running the fully adjusted model, an unadjusted model was run and then a semi-adjusted model was run that controlled for demographic features alone.

3.8. Sensitivity Analysis

To ensure that our results were robust, we performed two additional sets of analyses. First, to address the possibility that participants who were depressed at baseline might differ from those who subsequently developed depression, we re-ran the models after excluding participants who were depressed at baseline. Second, we re-ran our models after imputation for the small amount of missing data for the CESD score,

MMSE, number of chronic conditions and frailty, collected during each of the 18 month assessments. Multiple imputation was used with 50 draws per missing observation. The imputations were conducted in a longitudinally sequential fashion. During imputation, decedents were removed after death to ensure that their covariates were only informative prior to death. This sequential imputation strategy retained the temporal order of the longitudinal data and prevented incorrect inference due to potential bias of non-temporal associations and effects of retaining descendents in the data imputation. All covariates used in the main model were used to develop the model with the imputed data. In the model using the imputed data, a categorical variable for MMSE, rather than a continuous variable was used. Participants with an MMSE score of <=24 were categorized as having cognitive impairment.

3.9. Power Calculation

Power calculations were performed using PASS software. For the linear model, we did a post-hoc analysis and estimated power using an inequality test of two proportions in a repeated measures design. For group sample sizes during interval 1 of 58 for those on an antidepressant and 679 not on an antidepressant, we achieved 100% power to detect a difference in the CESD change score of 2.44-points in a design with 5 repeated measurements having a Toeplitz covariance structure when the standard deviation is 0.27. For the transition model, we achieved 100% power using an inequality test of two proportions in a repeated measure design. Approximately 650 participants who have data at a minimum of 2 time-points. The power was estimated to detect an odds

ratio of 2.0 thereby denoting at least a 100% increase in the rate of transitioning from depressed to non-depressed (or from non-depressed to depressed).

All statistical tests were 2-tailed, and $P<0.05$ was considered statistically significant. Analyses were performed used using SAS statistical software, version 9.1[94] and SAS-callable SUDAAN release 9.0.3.

4. Results

4.1. Study Sample

The characteristics of the participants at each time point are provided in Table 1. At baseline, the mean age was 78.4 years, and two-thirds of participants were women. The average number of chronic conditions increased over time, from 1.75 at baseline to 2.34 at 90 months. Similarly, the proportion of frail participants increased from 43% at baseline to 56% by 90 months.

Table 1: Characteristics of Participants Over The Course of 90 Months.

Characteristic	Baseline (n=754)	18-mos (n=675)	36-mos (n=612)	54-mos (n=538)	72-mos (n=471)	90-mos (n=419)
Age, yrs.; Mean (SD)	78.4 (5.3)	79.6 (5.1)	80.9 (5.1)	82.2 (4.9)	83.7 (4.8)	84.8 (4.7)
Race, Non-white; N (%)	72 (9.6)	69 (9.8)	64 (10.0)	58 (10.3)	54 (10.8)	49 (11.1)
Female; N (%)	487 (64.6)	439 (65.0)	405 (66.2)	359 (66.7)	310 (65.8)	281 (67.1)
Education, yrs; Mean (SD)	12 (2.9)	12 (2.9)	12 (2.8)	12 (2.9)	12.1 (2.8)	12 (2.8)
No. of chronic conditions;[a] Mean (SD)	1.75 (1.2)	1.95 (1.3)	2.06 (1.3)	2.14 (1.3)	2.26 (1.3)	2.34 (1.3)
Cognitive status;[b] Mean (SD)	26.8 (2.5)	26.4 (2.9)	26.3 (3.4)	25.5 (3.9)	25.3 (4.7)	25.2 (4.8)
Frailty; N(%)	322 (42.7)	287 (42.5)	265 (43.3)	265 (49.4)	259 (55.0)	234 (56.1)
Depression;[c] N(%)	100 (13.3)	116 (17.2)	124 (20.3)	109 (20.3)	91 (19.1)	98 (23.4)

a. The 9 self-reported, physician-diagnosed chronic conditions included hypertension, myocardial infarction, congestive heart failure, stroke, diabetes mellitus, hip fracture, arthritis, chronic lung disease, and cancer (other than minor skin cancer).
b. As assessed by the Mini-Mental State Examination (MMSE).
c. CESD score $\geq$20

4.2. Participants with Depressive Symptoms

A total of 100 participants (13.3%) were depressed (i.e., had a CESD score of ≥20) at baseline. The proportion of participants who were depressed increased over time, such that at 90-months 23% of participants were depressed. As indicated in Table 2, the mean age and the proportion of non-white participants were similar for those with and without depression at all time points. Participants with depression were more likely to be women, have less education and report a higher number of chronic conditions. Depressed participants were also nearly twice as likely to be frail as compared with non-depressed participants. Cognitive status was lower among depressed participants at each time point, with the exception of the 54-month time-point.

Table 2: Characteristics of Study Participants Over the Course of 90 Months According to Depression.

Characteristic	Baseline (n=754)			18-mos (n=675)			36-mos (n=612)		
	Depression[a]			Depression[a]			Depression[a]		
	YES (n=100)	NO (n=654)	p-value	YES (n=116)	NO (n=559)	p-value	YES (n=124)	NO (n=488)	p-value
Age, y	78.6(5.4)	78.4(5.2)	0.79	80.4(5.42)	79.5 (5.0)	0.10	81.6(5.3)	80.7 (5.0)	0.09
Female Sex[b]	86 (86.0)	401(61.3)	<.001	99 (85.3)	340(60.8)	<.001	102(82.3)	303(62.1)	<.001
Race, non-white[b]	14 (14.0)	58 (8.9)	0.10	10 (8.6)	56 (10.0)	0.65	14 (11.3)	48 (9.8)	0.63
Education	11.1(2.7)	12.1 (2.9)	<.001	10.9 (2.8)	12.2 (2.8)	<.001	11.1 (2.6)	12.2 (2.8)	<.001
No. of chronic conditions	2.08(1.4)	1.7 (1.2)	0.004	2.2 (1.32)	1.9 (1.2)	0.039	2.4 (1.4)	2.0 (1.2)	<.001
Cognitive status	26.0(2.8)	26.9 (2.4)	0.002	25.4 (3.2)	26.6 (2.8)	<.001	25.4 (3.5)	26.5 (3.3)	0.002
Frailty	62 (62.0)	260(39.8)	<.001	72 (62.1)	215(38.5)	<.001	84 (67.7)	181(37.1)	<.001
CESD score	24.8(4.8)	6.6 (6.1)	***	26.1 (6.5)	7.1(6.1)	***	24.9 (5.3)	7.3 (5.9)	***

Characteristic	54-mos (n=538)			72-mos (n=471)			90-mos (n=419)		
	Depression[a]			Depression[a]			Depression[a]		
	YES (n=109)	NO (n=429)	p-value	YES (n=91)	NO (n=380)	p-value	YES (n=98)	NO (n=321)	p-value
Age, y	82.7 (4.9)	82.0 (4.9)	0.19	84.3 (5.1)	83.6 (4.7)	0.19	85.3 (4.9)	84.7 (4.6)	0.25
Female Sex[b]	96 (88.1)	263(61.3)	<.001	74 (81.3)	236(62.1)	<.001	77 (78.6)	204(63.6)	<.001
Race, non-white[b]	13 (11.9)	42 (9.8)	0.52	8 (8.8)	40 (10.5)	0.62	10 (10.2)	38 (11.9)	0.64
Education	11.1 (2.8)	12.2 (2.8)	<.001	11.2 (2.7)	12.3 (2.8)	<.001	11.1 (2.9)	12.3 (2.8)	<.001
No. of chronic conditions	2.5 (1.5)	2.0 (1.2)	<.001	2.7 (1.3)	2.2 (1.3)	<.001	2.7 (1.3)	2.2 (1.3)	0.002
Cognitive status	24.9 (4.3)	25.6 (3.8)	0.12	23.6 (5.6)	25.7 (4.3)	<.001	23.3 (6.0)	25.8 (4.3)	<.001
Frailty	76 (69.7)	189(44.1)	<.001	65 (71.4)	194(51.1)	<.001	72 (73.5)	162(50.5)	<.001
CESD	26.1(5.9)	7.3 (6.1)	***	25.2(5.75)	8.4 (6.2)	***	26.3 (6.3)	8.2 (6.0)	***

a. Depression is defined as a CESD score $\geq$ 20.
b. Rate reported

4.3. Antidepressant Use

As shown in Figure 1, at any given time-point, approximately 10-15% of the study population was taking an antidepressant medication. The proportion of participants taking an antidepressant increased at each successive time-point, with the exception of 90 months where the rate approximated that of at 54-months.

Figure 1: Participants Taking an Antidepressant at Each Time-Point.

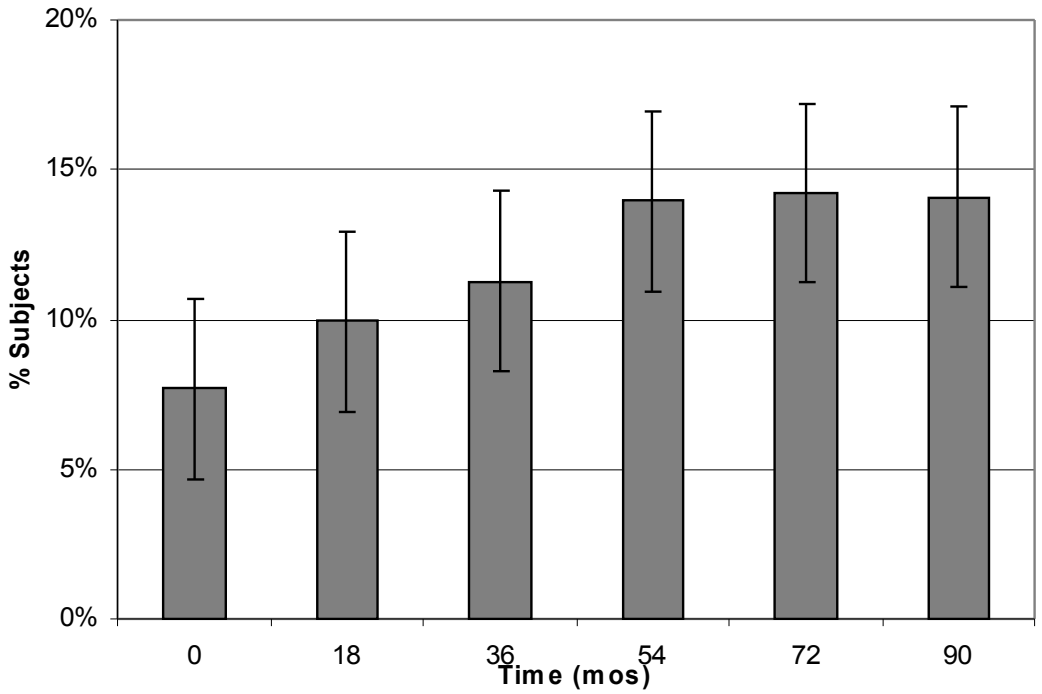


Table 3 presents the breakdown of categories of antidepressants reported by the study participants at each time-point. At baseline, there were 40(69%) out of 58 antidepressant medications were for SSRI's the remaining antidepressant medications were TCA's or Non-SSRI/Non-TCA antidepressants. At 90-months, 48 (72.2%) of the 66 antidepressant medications were SSRI's and 14(21.2%) of the antidepressant medications

were non-SSRI/non-TCA antidepressant medication. The decline in TCA antidepressant medications from baseline to 90-months was 19.8%.

Table 3: Antidepressant Medications Ascertained at Each Time-Point[a]

Antidepressants	**Baseline N=58 N (%)**	**18-mos N= 71 N (%)**	**36-mos N= 82 N (%)**	**54-mos N= 88 N (%)**	**72-mos N= 83 N (%)**	**90-mos N= 66 N (%)**
TCA's						
Desipramine	2 (3.4)	2 (2.8)	0 (0)	0 (0)	0 (0)	0 (0)
Doxepin	1 (1.7)	0 (0)	1 (1.2)	0 (0)	0 (0)	1 (1.5)
Imipramine	2 (3.4)	3 (4.2)	4 (4.9)	2 (2.3)	2 (2.4)	2 (3.0)
Nortriptyline	10 (17.0)	6 (8.5)	5 (6.1)	3 (3.4)	2 (2.4)	1 (1.5)
TCA %Total	**15 (25.9)**	**11 (15.5)**	**10 (12.2)**	**5 (5.7)**	**4 (4.8)**	**4 (6.1)**
SSRI's						
Citalopram	1 (1.7)	5 (7.0)	13 (15.9)	14 (15.9)	9 (10.8)	10 (15.2)
Escitalopram	0 (0)	0 (0)	0 (0)	3 (3.4)	14 (16.9)	10 (15.2)
Fluoxetine	8 (13.6)	12 (16.9)	10 (12.2)	11 (12.5)	7 (8.4)	4 (6.1)
Paroxetine	14 (23.7)	10 (14.1)	15 (18.3)	12 (13.6)	9 (10.8)	9 (13.6)
Sertraline	14 (23.7)	25 (35.2)	22 (26.8)	20 (22.7)	21 (25.3)	15 (22.7)
Serzone	3 (5.1)	1 (1.4)	0 (0)	1 (1.1)	0 (0)	0 (0)
SSRI %Total	**40 (69.0)**	**53 (74.6)**	**60 (73.1)**	**61 (69.3)**	**60 (72.3)**	**48 (72.7)**
Non-SSRI/Non-TCA						
Bupropion	0 (0)	3 (4.2)	2 (2.4)	9 (10.2)	7 (8.4)	4 (6.1)
Duloxetine	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.2)	1 (1.5)
Mirtazapine	0 (0)	2 (2.8)	6 (7.3)	7 (8.0)	6 (7.2)	4 (6.1)
Venlafaxine	3 (5.2)	2 (2.8)	4 (4.9)	6 (6.8)	5 (6.0)	5 (7.6)
Non-SSRI/Non-TCA *%Total*	**3 (5.2)**	**7 (9.9)**	**12 (14.6)**	**22 (25.0)**	**19 (22.9)**	**14 (21.2)**

N= Reflects number of antidepressants and not number of participants because some participants could be taking more than 1 antidepressant.

Table 4 presents the characteristics of the study population at each time point according to antidepressant use. Age, race and education did not differ significantly between those taking and not taking an antidepressant at any time point. Women were more likely to be taking an antidepressant than men ($p<0.05$), although there was not a significant gender difference at 72 or 90 months. At 54-months and 72-months,

participants taking an antidepressant were more likely to have a greater number of chronic conditions than those not taking an antidepressant. At each time point, with the exception of baseline, participants taking an antidepressant were more likely to have lower cognitive scores as assessed by the MMSE ($p<0.05$). At most time-points except at baseline and 18-months, participants taking an antidepressant were more likely to be frail than those not taking an antidepressant ($p<0.05$). In addition, those taking antidepressants had a higher depressive symptoms score than those not taking an antidepressant ($p<0.05$).

Table 4: Characteristics of Study Participants Over 90 Months by Antidepressant Use.

Characteristic	Baseline (n=754) Antidepressant[a]			18-mos (n=675) Antidepressant[a]			36-mos (n=612) Antidepressant[a]		
	YES (n=58)	NO (n=679)	p-value	YES (n=68)	NO (n=594)	p-value	YES (n=76)	NO (n=532)	p-value
Age, y	77.8(5.3)	78.5(5.3)	0.26	79.3(4.9)	79.7(5.1)	0.36	80.7(5.4)	80.9(5.0)	0.51
Female Sex	56 (74.7)	431(63.5)	0.03	62 (76.5)	377(63.5)	0.03	59 (73.8)	346(65.0)	0.03
Race,non-white	4 (6.9)	68 (9.8)	0.47	6 (8.8)	63 (9.8)	0.79	4 (5.3)	60 (10.6)	0.14
Education	12.0(2.5)	12.0 (2.9)	0.67	11.8(2.8)	12.0 (2.9)	0.30	12.0(2.7)	12.0 (2.9)	0.35
No.of chronic conditions	1.92(1.2)	1.73 (1.2)	0.29	2.04(1.3)	1.93 (1.2)	0.55	2.06(1.3)	2.03 (1.3)	0.16
Cognitive status	26.7(2.3)	26.8 (2.5)	0.71	25.7(3.7)	26.5 (2.8)	0.03	25.8(4.5)	26.3 (3.2)	0.03
Frailty	27 (46.6)	295(43.4)	0.54	35 (51.5)	258(43.4)	0.14	49 (64.5)	230(43.2)	<.001
Depression[c]	17 (29.3)	83(12.2)	<.001	27 (39.7)	89 (15.0)	<.001	24 (31.6)	100(18.8)	0.001
CESD	15.1(9.2)	8.5 (8.3)	<.001	17.9(10.3)	9.5 (9.0)	<.001	16.0(9.1)	10.2 (9.0)	<.001
	54-mos (n=538) Antidepressant[a]			**72-mos (n=471) Antidepressant[a]**			**90-mos (n=419) Antidepressant[a]**		
	YES (n=79)	NO (n=454)	p-value	YES (n=79)	NO (n=390)	p-value	YES (n=63)	NO (n=352)	p-value
Age, y	82.4(4.9)	82.1 (4.9)	0.90	84.0 (5.0)	83.7 (4.7)	0.60	84.8(4.7)	84.8 (4.6)	0.49
Female Sex	65 (77.4)	294(64.8)	0.01	63 (77.8)	247(63.3)	0.08	47 (70.1)	234(66.5)	0.68
Race,non-white	7 (8.9)	51 (10.5)	0.65	6 (7.6)	48 (11.4)	0.32	7 (11.1)	42 (11.2)	0.98
Education	11.6(2.8)	12.1 (2.9)	0.12	11.9 (2.6)	12.1 (2.8)	0.69	12.0(2.7)	12.0 (2.9)	0.73
No.of chronic conditions	2.1 (1.3)	2.1 (1.3)	0.02	2.59 (1.4)	2.19 (1.2)	0.01	2.5 (1.3)	2.3 (1.3)	0.46
Cognitive status	24.3(5.4)	25.7 (3.5)	0.01	23.5 (6.4)	25.6 (4.2)	0.002	24.1(5.8)	25.4 (4.6)	0.03
Frailty	52 (65.8)	231(50.9)	0.004	57 (72.2)	221(56.7)	0.002	42 (66.7)	210(59.7)	0.11
Depression[c]	35 (44.3)	74 (16.3)	<.001	29 (36.7)	62 (15.9)	<.001	22 (34.9)	76 (21.6)	0.005
CESD	17.6(10.5)	10.1 (9.1)	<.001	16.6(10.1)	10.7 (8.5)	<.001	16.8(10.9)	11.7 (9.5)	<.001

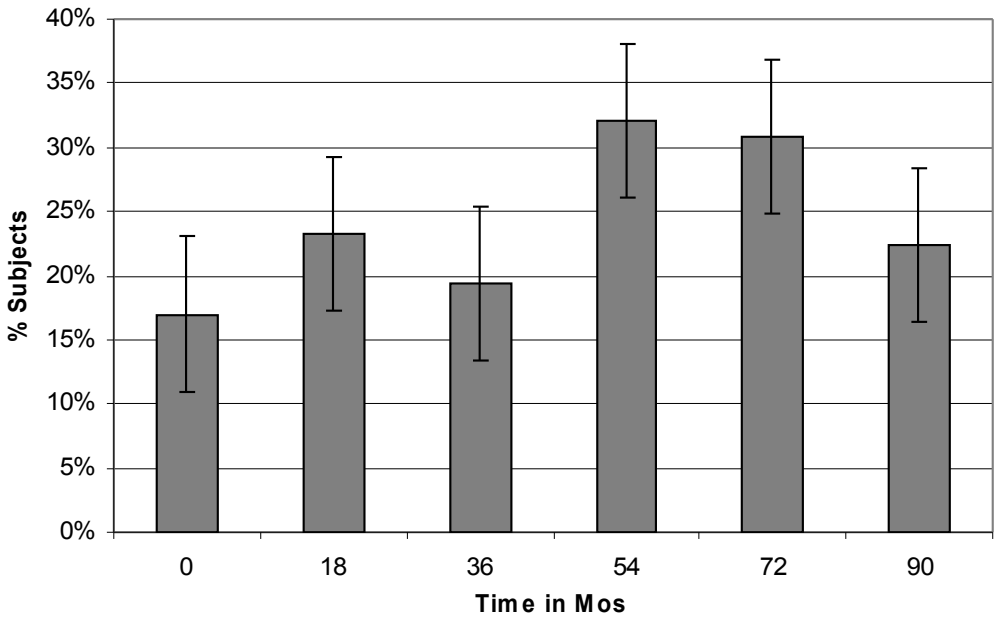
a. See list of medications that qualified as antidepressants in Table 3.

b. Participants with a CESD score $\geq$ 20.

c. Rate reported.

Of the 100 participants with depression (i.e., CESD≥20) at baseline, 17 (17%) were taking an antidepressant. Between 17-31% of the depressed participants were taking an antidepressant during the 90-month time period, as illustrated in Figure 2.

Figure 2: Participants with Depression Taking an Antidepressant.



4.4. Depression Change Score at Each Interval

Table 5 presents the association between antidepressant use and the change in depressive symptoms at each interval. In the unadjusted model, antidepressant use was not associated with a change in the CESD score, with the exception of interval 2 where antidepressant use was associated with an improvement in CESD score. These results did not change after adjusting for the demographic features. However, after adjusting for the demographic and clinical covariates, antidepressant use was associated with worsening of

depressive symptoms for each interval except interval 2. These associations were statistically significant for intervals 1, 3 and 5.

Table 5: Association Between Antidepressant Use and Change in Depressive Symptoms at Each Interval.

	Estimate (ß)	Standard error	P-value
Unadjusted			
Interval 1	0.16	1.08	0.88
Interval 2	-4.69	1.04	<0.001
Interval 3	0.86	1.18	0.47
Interval 4	-2.08	1.08	0.05
Interval 5	0.86	0.86	0.43
Adjusted for demographics[a]			
Interval 1	0.16	1.08	0.88
Interval 2	-4.71	1.05	<0.001
Interval 3	0.84	1.19	0.48
Interval 4	-2.01	1.08	0.07
Interval 5	0.75	1.08	0.49
Adjusted for demographics[a] and clinical covariates[b]			
Interval 1	2.3	1.1	0.03
Interval 2	-1.3	0.99	0.19
Interval 3	2.7	1.1	0.02
Interval 4	1.1	1.0	0.29
Interval 5	2.5	1.0	0.01

Note: The Parameter estimate (i.e. ß) indicates the magnitude of change in depressive symptoms, with a positive number indicating worsening of symptoms and a negative number indicating an improvement of symptoms

a. Demographics= age, race, gender, education

b. Clinical Covariates = number of chronic conditions, MMSE score, frailty (y/n) and CESD score at the beginning of each interval

4.5. Change Score/Mixed-effects Linear Longitudinal Regression

Table 6 presents the results from the final model evaluating the association between antidepressant use and change in depressive symptoms over time. Overall, antidepressant use was associated with an increase in depressive symptoms (i.e. the

change in the CESD score worsened, on average, by 2.22 points). However, this association was not statistically significant.

Table 6: The Longitudinal Association Between Antidepressant Use and Change in Depressive Symptoms by Mixed-Effects Linear Longitudinal Regression.

Fixed effects	Estimate (ß)	Standard error	P-value
Antidepressant use (yes)	2.22	0.99	0.14
Age (years)	0.01	0.02	0.81
Gender (female)	0.39	0.19	0.04
Education (years)	-0.06	0.04	0.08
Race (white)	0.57	0.29	0.05
CESD at beginning of each interval	-0.15	0.01	<0.001
Number of chronic conditions	0.34	0.07	<0.001
Frailty (yes)	0.04	0.25	0.88
MMSE (continuous score)	-0.13	0.04	<0.001
-2 Log-likelihood	17392.6		
Akaike Information Criterion (AIC)	17402.6		

ß: linear longitudinal regression coefficient, fixed effect: reflects the mean of the overall criteria
P-value for the intercept is a solution from the fixed effects; all other p-values are from the type 3 tests of fixed effects.

4.6. Transitions Rates at Each Interval

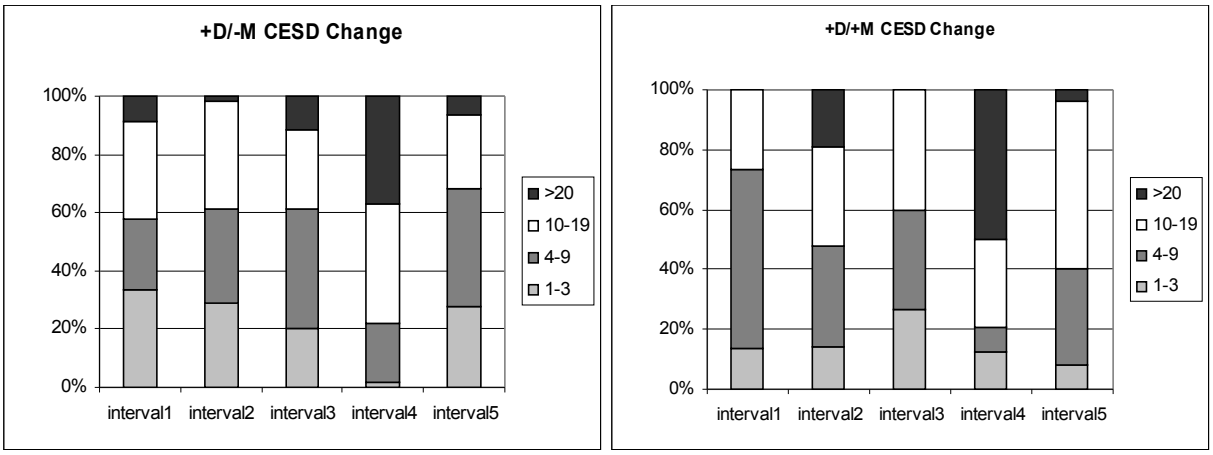
Table 7A presents transition rates not adjusted for covariates, according to antidepressant use, for persons who transitioned from a depressed state to either a non-depressed state or remained depressed. At each time point, there was not a significant association between antidepressant use and transitioning from a depressed state to a non-depressed state. Antidepressant use also was not associated with depressed participants remaining depressed.

Table 7A: Transition Rates Between the Three Outcome States Over Time According to Antidepressant Use.

	Interval 1 Antidepressant Use		Interval 2 Antidepressant Use		Interval 3 Antidepressant Use		Interval 4 Antidepressant Use		Interval 5 Antidepressant Use	
Transitions	**Yes (N=16)**	**No (N=75)**	**Yes (N=25)**	**No (N=84)**	**Yes (N=23)**	**No (N=96)**	**Yes (N=33)**	**No (N=70)**	**Yes (N=28)**	**No (N= 61)**
Depressed										
To Nondepressed										
N (%)	4 (25.0)	27 (36)	11(44)	30(35.7)	6 (26.1)	42(43.8)	10(30.3)	27(38.6)	10(35.7)	17(27.9)
p-value	0.46		0.50		0.12		0.42		0.49	
To Depressed										
N (%)	12(75.0)	40(53.3)	12(48)	42(50.0)	13(56.5)	42(43.8)	17(51.5)	35(50.0)	16(57.1)	37(60.7)
p-value	0.09		0.80		0.28		0.90		0.68	
To Death										
N (%)	0 (0)	8 (10.7)	2 (8.0)	12(14.3)	4 (17.4)	12(12.5)	6 (18.2)	8 (11.4)	2 (7.1)	7 (11.5)
p-value	0.18		0.40		0.54		0.36		0.51	

As shown in Figure 3A, most transitions from a depressed state to a non-depressed state were based on moderate to large absolute changes in the CESD score (ie, ≥10); small changes in the range of 1 to 3 points were observed for no more than 30% of the transitions during any of the 18-month intervals.

Figure 3A: The Absolute Change in CESD Scores For Participants that Transitioned from a Depressed State to a Non-depressed State.



+D/-M: Those initially depressed and not taking an antidepressant medication
+D/+M: Those initially depressed and taking and antidepressant medication
The key refers to the absolute change in the CESD.

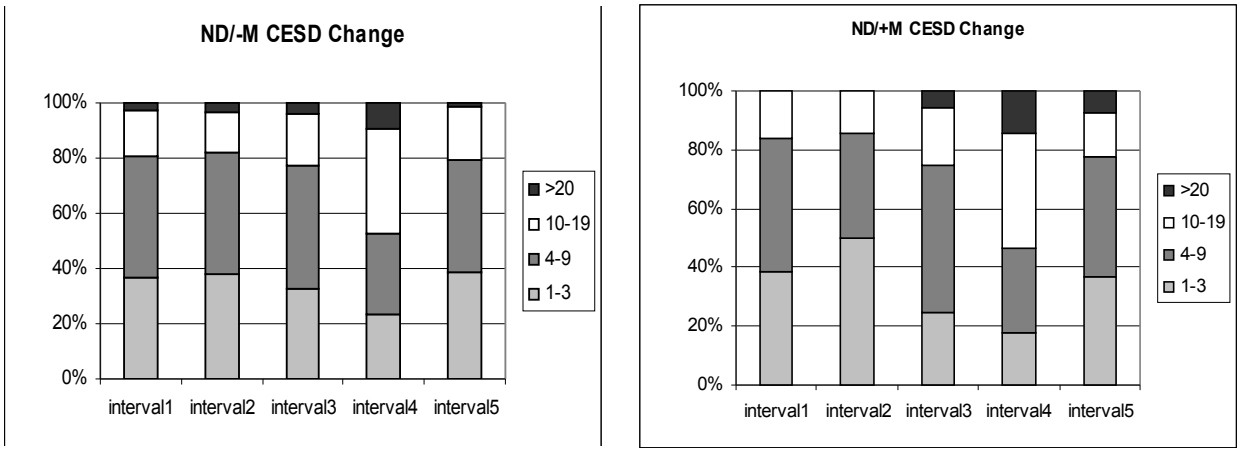
Table 7B presents transition rates not adjusted for covariates, according to antidepressant use, for persons who transitioned from a non-depressed state to either a depressed state or remained non-depressed. Among the non-depressed, antidepressant use was associated with a higher likelihood of remaining non-depressed at each interval, with the exception of interval 2. Participants who were initially not depressed and on an antidepressant were more likely to transition to a depressed state for 2 of the 5 intervals.

Table 7B: Transition Rates Between the Three Outcome States Over Time According to Antidepressant Use

	Interval 1 Antidepressant Use		Interval 2 Antidepressant Use		Interval 3 Antidepressant Use		Interval 4 Antidepressant Use		Interval 5 Antidepressant Use	
Transitions	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Nondepressed To Nondepressed	(N=38)	(N=592)	(N=35)	(N=506)	(N=45)	(N=427)	(N=58)	(N=448)	(N=38)	(N=330)
N (%)	28(73.7)	500(84.5)	30(85.7)	412(81.4)	28(62.2)	349(81.7)	40(69.0)	388(86.6)	24(63.2)	268(81.2)
p-value	0.04		0.51		0.01		<0.001		0.001	
To Depressed										
N (%)	7 (18.4)	57 (9.6)	3 (8.6)	64 (12.6)	10(22.2)	41 (9.6)	9 (15.5)	29 (6.5)	8 (21.1)	32 (9.7)
p-value	0.10		0.36		0.01		0.002		0.06	
To Death										
N (%)	3 (7.9)	35 (5.9)	2 (5.7)	30 (5.9)	7 (15.6)	37 (8.7)	9 (15.5)	31 (6.9)	6 (15.8)	30 (9.1)
p-value	0.67		0.84		0.11		0.003		0.26	

As shown in Figure 3B, most transitions from a non-depressed state to a depressed state were based on moderate to large absolute changes in the CESD score (ie, ≥10); small changes in the range of 1 to 3 points were observed for no more than 50% of the transitions during any of the 18-month intervals.

Figure 3B: The Absolute Change in CESD Scores For Participants that Transitioned from a Non-depressed State to a Depressed State.



ND/-M: Those initially not depressed and not taking an antidepressant medication
ND/+M: Those initially not depressed and taking and antidepressant medication
The key refers to the absolute change in the CESD.

4.7. Generalized Estimating Equations Models

Table 8 presents the unadjusted and adjusted odds ratios from the longitudinal models evaluating the association between antidepressant use and the likelihood of transitioning between the three outcome states, among those who were depressed at the beginning of each interval. Antidepressant use was not associated with a transition from a depressed state to a non-depressed state over time, meaning that participants taking an antidepressant were no more likely to transition to a non-depressed state than they were to remain depressed, even after adjusting for demographics and the clinical covariates.

Table 8: Association Between Antidepressant Use and Transitions Over the Course of 7.5 Years in Initially Depressed Participants.

	Odds Ratio	95% CI
Unadjusted		
Depressed	1	--
Not Depressed	0.78	0.5-1.2
Dead	0.83	0.4-1.8
Adjusted for demographics[a]		
Depressed	1	--
Not Depressed	0.80	0.5-1.3
Dead	0.90	0.4-2.0
Adjusted for demographics[a] and clinical covariates[b]		
Depressed	1	--
Not Depressed	0.85	0.5-1.4
Dead	0.49	0.2-1.2

Note: The Parameter estimate indicates the magnitude of change in depressive symptoms and a positive number indicates worsening of symptoms, while a negative number indicates an improvement of symptoms

a. Demographics= age, race, gender, education

b. Clinical Covariates = number of chronic conditions, MMSE score, frailty (y/n) and CESD score at the beginning of each interval

Table 9 presents the unadjusted and adjusted odds ratios from the longitudinal models evaluating the association between antidepressant use and the likelihood of transitioning between the three outcome states, among those who were non-depressed at the beginning of each interval. Results from the unadjusted model indicate that those taking an antidepressant were more likely to transition from a non-depressed to a depressed state, than to remain non-depressed (OR 2.01, 95% CI 1.3-3.0). This finding persisted after adjustment for demographic (OR 1.9, 95% CI 1.2-2.9) and clinical covariates (OR 1.79, 95% CI 1.2-2.8).

Table 9: Association Between Antidepressant Use and Transitions Over the Course of 7.5 Years in Initially Non-depressed Participants.

	Odds Ratio	95% CI
Unadjusted		
Not Depressed	1	--
Depressed	2.01	1.3-3.0
Dead	2.29	1.4-3.7
Adjusted for demographics		
Not Depressed	1	--
Depressed	1.90	1.2-2.9
Dead	2.46	1.5-4.0
Adjusted for demographics and clinical covariates		
Not Depressed	1	--
Depressed	1.79	1.2-2.8
Dead	1.80	1.1-3.0

Note: The Parameter estimate indicates the magnitude of change in depressive symptoms and a positive number indicates worsening of symptoms, while a negative number indicates an improvement of symptoms

a. Demographics= age, race, gender, education

b. Clinical Covariates = number of chronic diseases, MMSE score, frailty (y/n) and CESD score at the beginning of each interval

4.8. Sensitivity Analysis

4.8.1. Eliminating Participants Who Were Depressed at Baseline

Table 10 indicates that when participants with elevated depressive symptoms at baseline were omitted from the analysis, use of an antidepressant medication was still not associated with a change in depression scores.

Table 10 : The Longitudinal Association Between Antidepressant Use and Change in Depressive Symptoms by Mixed-Effects Linear Longitudinal Regression, Excluding Participants Who Were Depressed at Baseline.

Fixed effects	**Estimate (ß)**	**Standard error**	**P-value**
Antidepressant use (yes)	1.30	1.06	0.21
Age (years)	0.0006	0.02	0.98
Gender (female)	0.35	0.19	0.08
Education (years)	-0.06	0.04	0.12
Race (white)	0.44	0.32	0.17
CESD at beginning of each interval	-0.16	0.01	<0.001
Number of chronic conditions	0.34	0.08	<0.001
Frailty (yes)	0.05	0.27	0.87
MMSE (continuous score)	-0.13	0.04	0.002
-2 Log-likelihood	15210.7		
Akaike Information Criterion (AIC)	15220.7		

ß: linear longitudinal regression coefficient, fixed effect: reflects the mean of the overall criteria

P-value for the intercept is a solution from the fixed effects; all other p-values are from the type 3 tests of fixed effects.

As shown in Table 11, for participants who started an interval in a depressed state, antidepressant use was not associated with the transition from depression to a non-depressed state. These findings persisted after adjusting for demographic and clinical covariates.

Table 11: Association Between Antidepressant Use and Change in Depressive Symptoms at Each Interval, in Initially Depressed Participants; Omitting Participants Who Were Depressed at Baseline.

	Odds Ratio	95% CI
Unadjusted		
Depressed	1	--
Not Depressed	0.77	0.4-1.5
Dead	0.71	0.2-2.2
Adjusted for demographics		
Depressed	1	--
Not Depressed	0.84	0.4-1.7
Dead	0.87	0.3-3.0
Adjusted for demographics and clinical covariates		
Depressed	1	--
Not Depressed	0.57	0.4-1.7
Dead	0.49	0.1-1.9

The results are from 4 intervals since we eliminated participants who had depression at baseline

Note: The Parameter estimate indicates the magnitude of change in depressive symptoms and a positive number indicates worsening of symptoms, while a negative number indicates an improvement of symptoms

a. Demographics= age, race, gender, education

b. Clinical Covariates = number of chronic diseases, MMSE score, frailty (y/n) and CESD score at the beginning of each interval

Table 12 provides the results of the generalized estimating equation (GEE) model evaluating participants who were not depressed at baseline. Similar to the GEE results from the original models, participants taking an antidepressant were more likely to transition from a non-depressed state to a depressed state rather than to stay non-depressed. This finding persisted after adjustment for the demographic and the clinical covariates (OR=2.43, 95% CI 1.3-4.5).

Table 12: Association Between Antidepressant Use and Change in Depressive Symptoms at Each Interval, in Initially Not Depressed Participants; Omitting Participants Who Were Depressed at Baseline.

	Odds Ratio	95% CI
Unadjusted		
Not Depressed	1	--
Depressed	2.60	1.5-4.6
Dead	2.82	1.6-5.1
Adjusted for demographics		
Not Depressed	1	--
Depressed	2.51	1.4-4.5
Dead	2.96	1.6-5.4
Adjusted for demographics and clinical covariates		
Not Depressed	1	--
Depressed	2.43	1.3-4.5
Dead	2.19	1.1-4.3

Note: The Parameter estimate indicates the magnitude of change in depressive symptoms and a positive number indicates worsening of symptoms, while a negative number indicates an improvement of symptoms

a. Demographics= age, race, gender, education

b. Clinical Covariates = number of chronic diseases, MMSE score, frailty (y/n) and CESD score at the beginning of each interval

4.8.2. Imputed Data

The results did not change appreciably after imputation for missing data. Using imputed data for the CESD at the beginning of each interval, number of chronic conditions, frailty and cognitive status as shown in Table 13, antidepressant use was not associated with change in depressive symptoms over time (ß=2.44; SE 0.91; p=0.08).

Table 13: The Longitudinal Association Between Antidepressant Use and Change in Depressive Symptoms by Mixed-Effects Linear Longitudinal Regression, Imputed Data Results.

Fixed effects	**Estimate (ß)**	**Standard error**	**P-value**
Antidepressant use (yes)	2.44	0.91	0.08
Age (years)	-0.07	0.02	0.73
Gender (female)	0.23	0.18	0.22
Education (years)	-0.07	0.03	0.04
Race (white)	0.59	0.28	0.04
CESD at beginning of each interval*	-0.15	0.01	<0.001
Number of chronic conditions*	0.29	0.07	<0.001
Frailty (yes)*	0.43	0.22	0.04
MMSE (no cognitive deficit)*	0.85	0.30	0.004
-2 Log-likelihood	18435.7		
Akaike Information Criterion (AIC)	18445.7		

ß: linear longitudinal regression coefficient, fixed effect: reflects the mean of the overall criteria
P-value for the intercept is a solution from the fixed effects; all other p-values are from the type 3 tests of fixed effects.
*imputed variables

Similarly, antidepressant use was not associated with a transition from a depressed state to a non-depressed state, over time, among those participants who were depressed at the beginning of each interval (Table 14); but as shown in Table 15 antidepressant use was associated with a transition from a non-depressed state to a

depressed state, over time, among those participants who were non-depressed at the beginning of each interval (OR 1.80, 95% CI 1.2-2.8).

Table 14: Association Between Antidepressant Use and Change in Depressive Symptoms at Each Interval, in Initially Depressed Participants, *Imputed Data Results.*

	Odds Ratio	95% CI
Unadjusted		
Depressed	1	--
Not Depressed	0.78	0.5-1.2
Dead	0.84	0.4-1.8
Adjusted for demographics		
Depressed	1	--
Not Depressed	0.82	0.5-1.3
Dead	0.93	0.4-1.4
Adjusted for demographics and clinical covariates		
Depressed	1	--
Not Depressed	0.79	0.5-1.2
Dead	0.70	0.3-1.6

Note: The Parameter estimate indicates the magnitude of change in depressive symptoms and a positive number indicates worsening of symptoms, while a negative number indicates an improvement of symptoms

a. Demographics= age, race, gender, education

b. Clinical Covariates = number of chronic diseases, MMSE score, frailty (y/n) and CESD score at the beginning of each interval

Table 15: Association Between Antidepressant Use and Change in Depressive Symptoms at Each Interval, in Initially Not Depressed Participants, *Imputed Data Results.*

	Odds Ratio	95% CI
Unadjusted		
Not Depressed	1	--
Depressed	2.02	1.3-3.0
Dead	2.30	1.4-3.7
Adjusted for demographics		
Not Depressed	1	--
Depressed	1.88	1.2-2.9
Dead	2.33	1.4-3.8
Adjusted for demographics and clinical covariates		
Not Depressed	1	--
Depressed	1.80	1.2-2.8
Dead	1.93	1.2-3.1

Note: The Parameter estimate indicates the magnitude of change in depressive symptoms and a positive number indicates worsening of symptoms, while a negative number indicates an improvement of symptoms

a. Demographics= age, race, gender, education

b. Clinical Covariates = number of chronic diseases, MMSE score, frailty (y/n) and CESD score at the beginning of each interval

5. Discussion

The treatment of depression and depressive symptoms in the older adult consists almost entirely of antidepressant medications prescribed in primary care settings. However, there is relatively little information on the efficacy or effectiveness of antidepressant medications on depressive symptoms in the community. Therefore, this longitudinal study of older adults in New Haven county sought to describe the use of antidepressant medications over time, to evaluate the association between antidepressant use and reduction in the severity of depressive symptoms over time, and to determine if antidepressant use was associated with transitioning from a depressed state to a non-depressed state. We found that most participants with depression were not taking antidepressant medications. Furthermore, antidepressant use was not associated with a reduction in the severity of depressive symptoms over time; nor was it associated with transitioning from a depressed state to a non-depressed state.

5.1. Potential Underdiagnosis and/or Undertreatment of Depression

During the 90-month follow-up, between 13% to 23% of the study participants had elevated depressive symptoms. These prevalence rates are slightly higher than the rates of 6% to 18% that have previously been reported in the literature.[2-6] Reasons for this may include the higher mean age and more diverse racial composition of our sample compared with the samples in these other studies.[95] Furthermore, the PEP study over-sampled participants who were physically frail. As prior studies have indicated that frailty is associated with depression, the higher prevalence of frailty in our study

population, as compared with other populations of community-dwelling older persons, may account for the higher rates of elevated depressive symptoms reported in our study.[17, 96]

5.2. Potential Undertreatment

At all time-points during the 90-month follow-up, more than 60% of participants with elevated depressive symptoms were not taking an antidepressant. Prior studies have indicated that depression in older adults is undertreated, such that, at most, no more than a third to half of patients who have been identified as depressed are treated by a physician by either/or pharmacological or non-pharmacological methods..[30, 47, 48,97-99] Studies evaluating antidepressant use in older adults with depression have reported rates ranging from 19% to 42%.[97-99] However, what we know about rates of antidepressant medication treatment primarily comes from studies of older adults with a clinical diagnosis of depression. In addition, with the exception of one study,[100] the published studies evaluating antidepressant use in older persons have been cross-sectional.[97-99] For example, Skoog et al. evaluated antidepressant medication treatment before the widespread use of SSRI's and found that 19% of older adults with depressive disorders and 24% of those with major depression were taking antidepressant medications.[97] Consequently, relatively little in known about the rates of antidepressant use in depressed older persons over time.

In the Longitudinal Aging Study Amsterdam (LASA)[101], antidepressant use was examined over 10 years, from 1992 to 2002, in a representative, community-based population of persons aged 55-85 years. The rate of antidepressant use ranged from 2%

to 5.3%. As in our study, antidepressant use increased over time in the population as a whole, and in the subgroups who had a depressive disorder. For example, the rate of antidepressant use increased from 2.9% to 12.1% among participants who had elevated depressive symptoms, defined as CESD ≥16, and from 15% to 30.4% among those who were clinically depressed.

Our study differs from the LASA study in a several ways. First, our study was conducted between 1998-2007, a period during which SSRI's were first-line therapy for depression. This is important because the rates of antidepressant use have increased since the introduction of SSRI's. Second, the LASA study population, which included only Dutch participants living in the Netherlands, was much more homogeneous than our population . Thus, the results may not generally applicable to a population in the United States. Third, the LASA study interviewed participants every 3 years for 12 years (4 time-points) , while we interviewed participants every 18 months for 7 ½ years (6 total time-points). At 90 months, however, there was a slight decline such that less than 25% of participants with elevated depressive symptoms were taking an antidepressant (see Figure 2 in results). Because we only have one time-point that demonstrates a decline in the rates of antidepressant use, it is difficult to infer the cause. However, this finding raises the question as to whether under treatment and under recognition of depression may occur more frequently in the old-old as compared with the young-old.

Depressive symptoms may go untreated because they are not recognized. Major depression goes unrecognized or underdiagnosed in approximately 60% of the older patients seen in primary care settings.[102, 103] In all adults major depression was unrecognized in 44% of patients, those with symptoms that were less severe were more

likely to have unrecognized depression.[104] While in the old-old (age>85) depression was unrecognized in 75% of the patients by a primary care physician.[105] In hospitalized geriatric patients, psychogeriatricians were able to identify 43% of cases of depression while the geriatricians only identified 19% of the cases.[106] Depression and depressive symptoms are missed in more then half of patient's in a variety of settings. Physicians may be better able to identify patients with greater degrees of depression, thus not identifying the majority of patients with elevated depressive symptoms who still may benefit from treatment.[107-109] While undertreatment of depression may be attributable to underrecognition of depression, we could not address this issue directly in the current study since we did not have access to medical records. Nonetheless, increased detection of depressive symptoms would likely lead to enhanced treatment of this disabling disorder, with potential benefits in quality of life and other health outcomes.

There have been some initiatives to increase screening of depressive symptoms in older adults by primary care physicians. In one study, primary care physicians were provided with information about diagnosing and treating depression in older adults.[75] Despite the increased detection and awareness of depression, this intervention did not lead to significant improvement of the patients.[75]

Overall, our findings highlight potential opportunities to enhance the identification of depression and to optimize medical treatment of depression among older adults.

5.3. Effectiveness of Antidepressants

Contrary to our hypothesis, we found that antidepressant use was not associated with a reduction in the severity of depressive symptoms. In fact, on average, depressive symptoms worsened among participants taking antidepressant medications. The consistency of our findings over 4 of the 5 different time intervals provides strong evidence that antidepressant use, as prescribed in clinical practice, is not associated with an improvement in depressive symptoms.

As noted in the Introduction, what we know about the effectiveness of antidepressant medications in older persons primarily comes from clinical trials that have included specialized populations such as those being treated in an in-patient setting, those being treated by a psychiatrist, or those who have been diagnosed with a clinical depressive disorder. Consequently, treatment recommendations are extrapolated from findings that may not be generalizable to the majority of older adults who have depressive symptoms .

We also evaluated transitions into and out of depression states at 18-month intervals for 7 1/2 . years, using longitudinal methods that enhanced our power to detect clinically meaningful differences. We found that antidepressant use was not associated with the transition from a depressed state to a non-depressed state. It has been estimated that only 40 to 65% of all adults, including older adults, have a favorable response to any given antidepressant.[110] In 4 out of the 5 time intervals, we found that less than 40% of the participants who were depressed and taking an antidepressant medication transitioned to a non-depressed state. In contrast, we found that non-depressed persons who were taking an antidepressant were more likely to transition to a depressed state.

There are several possible reasons why depressive symptoms did not improve despite treatment with an antidepressant. First, possible lack of adherence to the medical treatment is possible. Second, the dose of the antidepressant medications may have been too low**.** Third, the treatment duration may not have been long enough. Fourth, physicians may have prescribed antidepressant medication to patient's who were sicker.

It is possible that we found a worsening of depressive symptoms because there could have been a high degree of non-adherence.[111] Some variables that have been identified as being related to poor adherence include poorer social support[112], less non-family interaction, greater basic and instrumental activities of daily living limitations, poor self-rated health, higher baseline depression scores.[113] Of older persons who receive a prescription for an antidepressant, less than half fill the prescription.[29] Given the high prevalence of non-adherence, it is important to have a follow-up period within a couple of weeks to determine if the patient started the medication and if they are tolerating the medication.[29, 36]

It is also possible that primary care physicians did not achieve a therapeutic dose of the antidepressant medication. In a survey of primary care physicians in Ontario, Canada it was found many physicians were not willing to titrate the dose of their prescribed antidepressant medications beyond the lower half of the therapeutic range even when patients were tolerating the medications without side effects but were not responding to treatment.[114, 115] Another study found that only 56% of study participants were on an adequate dose of antidepressants.[115]

It is possible the treatment was sub-optimal in duration. Our 18-month time-period would have allowed enough time for the antidepressant to take effect; however

participants may not have been taking an antidepressant during the entire interview interval. Up to 12 weeks of treatment with antidepressant medications may be needed to elicit a full response and remission.[110, 116, 117] There is evidence indicating that improvement of symptoms of minor depression can occur independent of treatment, which is why one of the recommendations for treating minor depression is watchful waiting.[118, 119] However it is possible that physicians may not re-address the depressive symptoms, or that the patient does not follow-up in the recommended amount of time. Once therapy is initiated it may likely be sub-optimal in duration.

The observed worsening of depressive symptoms in participants on an antidepressant may be due to confounding by indication. Possible indications for antidepressant use can be a diagnosis of depression or related psychiatric disorders and depression severity. It may be that physicians readily identified those patients who had a past medical history of depression or a high degree of depressive symptoms. However, we controlled for the CESD score at the beginning of each interval for both the change score model and the transitions model. Indication bias can be controlled for by adjusting for a past history of depressive disorders and whether the patient had been on antidepressants in the past.

5.4. The Future for Depression Treatment in Older Adults

While under recognition of depression in older adults continues to be a problem, there are new healthcare models that may promote the delivery of better mental health care to this population. Studies have shown that collaborative care models that incorporate mental health specialty treatment into primary care settings, such as those

used in the Veterans' Affairs Primary Care, IMPACT and PROSPECT studies, result in significant improvements in depression outcomes for older primary care patients.[120-122] The Improving Mood Promoting Access to Collaborative Treatment (IMPACT) randomized those with major depression or dysthymia to usual primary care treatment or a collaborative treatment group (e.g. participants were assigned a case manager in addition to their medication and/or counseling). It was found that the patient's randomized to the collaborative treatment group had better outcomes and had lower health care costs.[121, 122] The Prevention of Suicide in Primary Care Elderly-Collaborative Trial study (PROSPECT) a specially trained master's level health specialist works with the primary care physician to identify and suggest treatments for depression in older patients, with a goal of increasing adherence to pharmacological treatment.[123-125] The goal of this study was to create a model that would reduce suicide in older adults and may be implemented in a primary care medical practices. Suicidal ideation was reduced regardless of depression severity in patients that participated in the PROSPECT trial.[126]

In 2007, an expert panel convened and strongly recommended that depression care management-modeled interventions be provided in primary care clinics.[127] There is strong evidence that the collaborative care models described above are effective. Future studies may want to include more training for physicians with respect to appropriate dosing and drug selection, more frequent and objective follow-up assessments, and the use of non-pharmacological (i.e. psychotherapy) treatment.. In addition, many of the studies described above were conducted in academic centers or clinics closely linked to an academic center, future studies would want to evaluate feasibility in a non-academic environment where resources may be limited.

5.5. Study Limitations

Some limitations of the study should be considered when interpreting the results. First, we did not have information about dosage, frequency, duration or changes in medication. However, we had information on who was taking an antidepressant at every 18-month time-point. Also**,** we had no information about adherence to medications. Future studies evaluating antidepressant effectiveness in older adults should include specific information about the antidepressant medication, dosage and adherence. This information would allow us to further categorize participants as having aggressive treatment, adequate treatment, or undertreatment of their depression. Because information regarding participants' depression status before the baseline interview was not available, we could not determine if participants' first transition from a non-depressed to a depressed state represents incident depression. We also do not know if a participant had major depression in the past. Consequently, it is possible that the depressed participants in our study that are not being treated have treatment resistant depression or depression that is not fully remitted. However, to control for this, we ran sensitivity analysis that excluded subjects who were depressed at baseline and obtained the same results. [29-31]

We also did not assess non-pharmacologic treatments of depression. Hence, our rates for depressant treatment may have been underestimates. However, very few older adults see a psychotherapist for their depression and this likely would not affect a large proportion of our participants. Future studies should include measures to assess these variables.

Because our assessments were completed every 18-months, it is possible that some participants were treated for depression between two time time-points and achieved remission before the next assessment. If brief treatments and remissions occurred at random with respect to the assessment intervals, we should have observed many of them, but would have underestimated the rate and effectiveness of the antidepressant treatment. Future studies would want to decrease the duration between interviews to 6-months to 1 year.

Because our study participants were members of a single health plan, initially nondisabled, and at least aged 70 years at baseline, the generalizability of our findings to other older adult populations may be questioned. However, the demographic characteristics of our study population, including years of education, closely mirror those of persons 70 years or older in New Haven County, Connecticut, which, in turn, are comparable to those in the United States as a whole, with the exception of race. New Haven County has more non- Hispanic whites in this age group than in the United States (91% versus 84%). Furthermore, generalizability depends not only on the characteristics of the study population but also on its stability over time. The high participation rate, completeness of data collection, and low rate of attrition for reasons other than death all enhance the generalizability of our findings and at least partially offset the absence of a population-based sample.

Finally, this was an epidemiologic study and not a clinical trial so inferences about treatment effectiveness must be made cautiously. Again, an unexpected finding was that antidepressant treatment was not associated with improvement of depressive symptoms, but was associated with worsening of depressive symptoms.

5.6. Conclusions and Recommendations

Our findings raise concerns about the effectiveness of antidepressant medications, as prescribed to older adults in clinical practice. The results of this study indicate that more research is needed to understand the role of antidepressant medications in older adults with elevated depressive symptoms.

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