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Comparative Cognitive Profile of Second-Generation Antidepressants in Elderly Nursing Home Residents With Depression

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Abstract

Background—Past literature suggests that the use of second-generation antidepressants improves cognition in depressed elderly patients.

Objective—This study assessed the comparative cognitive profile of commonly used second-generation antidepressant classes in elderly residents with depression.

Methods—A multiple propensity score adjusted retrospective cohort study was conducted using 2007–2010 Medicare Part D claims and Minimum Data Set (MDS). Elderly nursing home residents (65 years or older) with depression using a new prescription of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tetracyclics constituted the study cohort. The outcome of interest was cognition, measured using the MDS Cognition Scale. Cognition was measured at each quarterly assessment after antidepressant initiation for a maximum of 1 year. The propensity score–adjusted repeated-measures mixed model was used to evaluate the comparative profile of SSRIs, SNRIs, and tetracyclics with respect to cognition.

Results—The study cohort comprised 1518 elderly nursing home residents. Of these, 1081 received SSRIs (71.21%), 320 received tetracyclics (21.08%), and 117 received SNRIs (7.71%). The propensity score–adjusted repeated-measures mixed model did not show any statistically significant difference in cognition with the use of SSRIs (β = −0.14; 95% CI = −0.53, 0.25) or tetracyclics (β = −0.36; 95% CI = −0.80, 0.08) when compared with SNRIs, after controlling for other factors.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Conclusions—The cognitive effect of SSRIs, SNRIs, and tetracyclics was similar in elderly nursing home residents with depression. Further studies are needed to evaluate the long-term cognitive effects of second-generation antidepressants in this vulnerable population.

Keywords

second-generation antidepressants; cognition; depression; elderly; nursing home residents

Introduction

Depression is one of the most common diseases among the elderly population in long-term care.[1] Prevalence rates of depression in elderly nursing home residents are up to 5 times that in community-dwelling elderly.[2] Depression in later life is a major public health concern because it has a significant impact on quality of life as a result of impaired physical and cognitive functioning.[3,4] Residents with depression require more staff services and health care; and are at significant risk for 1-year mortality. Consequently, the Omnibus Budget Reconciliation Act of 1987 incorporated regulations to improve care for residents with depression.[5]

Patients with depression often present with significant cognitive complaints or deficits, including impairment in executive function, attention, memory, and processing of information.[6,7] A meta-analysis by Christensen et al.[8] revealed that depressed patients had lower performance on almost all cognitive tests. Specifically, depressed patients performed poorly on pleasant or neutral tasks when compared with unpleasant task, on speeded tasks when compared with nonspeeded tasks, and on vigilance tasks.[8] A recently published report found probable increased risks of cognitive decline caused by depression based on 13 studies with a follow-up of 1.5 to 5.6 years in later life.[9] Richard et al.[10] found that elderly patients with depression had a 40% higher risk of mild cognitive impairment and more than 2 times higher risk of dementia than patients without depression.

Antidepressants can improve neurocognitive function through their effects on depressive symptomatology and pharmacodynamic effects mediated by neurophysiological changes in the brain. Biringer et al.[11] found that paroxetine is associated with a lower performance on neurocognitive measures such as verbal recall scores and paired-associate learning scores; and sertraline has a better performance than the other selective serotonin reuptake inhibitors (SSRIs) on neurocognitive measures such as attention, memory, and tempo-demanding tasks. Additionally, serotonin-norepinephrine reuptake inhibitors (SNRIs) may be more beneficial with regard to cognitive function than other anti-depressants.[11] Francomano et al.[12] concluded that treatment with antidepressants, especially SSRIs and SNRIs, may offer a protective effect on cognitive impairment.

Two meta-analyses found that second-generation antidepressants are similar in their efficacy and effectiveness for treating depression.[13,14] However, these agents have different onset of action and adverse event profiles because of different receptor binding properties and sites of action,[13,14] which can lead to differential cognitive outcome. For example, SSRIs block the reuptake of 5-hydroxytryptamine receptors (5HT) and increase synaptic 5HT transmission.[15] Although SSRIs lack any muscarinic and histaminergic receptor activity,

some SSRIs like paroxetine can worsen cognitive impairment because of their anticholinergic activity[16] and are considered as potentially inappropriate for elderly patients with dementia and cognitive impairment.[17] However, a recent study did not find any higher risk of dementia among depressed elderly nursing home patients using paroxetine when compared with the other SSRIs.[18]

Tetracyclics such as mirtazapine act on both adrenergic (α2 antagonist) and serotonergic (5-HT2 antagonist) receptors. They can cause weight gain and sedation because of their strong antihistamine properties.[19] Maprotiline acts by blocking reuptake of norepinephrine (α1 and 5-HT2 antagonist). It can also cause sedation because of its strong antihistamine properties. SNRIs improve mood by blocking the reuptake of both norepinephrine and serotonin (5HT). Additionally, anticholinergic, sedative, or hypotensive side effects are not common with SNRIs.[20] Some studies also suggest that antidepressants yield little cognitive improvement in non-demented depressed older adults, and depression-related cognitive impairment may persist even after adequate treatment with antidepressants.[21–23]

Little is known about the comparative cognitive profile of different second-generation antidepressant classes in depressed elderly patients. Doraiswamy et al.[24] examined effects of antidepressants on cognitive functioning in depressed elderly patients. They used the Shopping List Task, which assesses short-term and long-term memory storage and retrieval,[25] and the Digit Symbol Substitution Test, which assesses visual tracking, motor performance, and coding.[26] They found improvement in cognitive function in elderly patients taking antidepressants, which was highest for sertraline followed by nortriptyline and fluoxetine.[24] Allain et al.[27] evaluated the comparative cognition effects of moclobemide, viloxazine, and maprotiline in young depressed patients. They did not find any differences in improvement in attention, memory, and psychomotor speed among the 3 groups.

A recent study evaluated the effects of antidepressant monotherapy on psychomotor functions related to cardriving skills in depressive patients. The researchers found that depressed patients using mirtazapine performed better than patients using TCAs, SSRIs, or venlafaxine on driving ability. However, there was no difference on psychomotor and visual tests.[28] It is unclear if pharmacological differences in second-generation antidepressant classes translate into differential effects on cognition, particularly in elderly nursing home residents, a population with a high prevalence of depression and risk of cognitive impairment. There is a strong need to understand comparative cognitive profiles of second-generation antidepressants, specifically SSRIs, tetracyclics, and SNRIs, because they are the most commonly prescribed antidepressants in depressed nursing home residents.[29,30] Therefore, this study evaluated the comparative cognitive effect of these 3 commonly used antidepressant classes in elderly nursing home residents with depression.

Material and Methods

Data Source

The present study used 2007–2010 Minimum Data Set (MDS) linked Medicare Part D data to achieve the research objective. Medicare Part D, launched in 2006, provides prescription

benefits for Medicare beneficiaries.[31] The MDS is a national standardized assessment tool for comprehensive assessment of residents in federally certified nursing home facilities.[32,33] Comprehensive MDS assessments are completed on each resident on admission and when the resident shows "significant change in status." A subset of the full MDS assessment is conducted quarterly. Quarterly assessments are brief in nature and are captured quarterly or following any adverse events.[34] Previous studies report strong interrater reliability and internal consistency of scales used for the assessment of nursing home residents.[35] This study was approved by the University of Houston Committee for the Protection of Human Subjects under the exempt category.

Study Design and Cohort

A retrospective cohort design involving propensity score adjustment was used to examine the comparative cognitive profile of 3 antidepressant classes in depressed elderly nursing home residents. Figure 1 outlines the definitions used to construct the study and comparison groups. Patients were classified as long-term residents if the difference between last admission and last annual assessment was ≥365 days. Use of the index antidepressant was defined as having a first prescription of an antidepressant without any prescription for any antidepressants in the past 6 months. The study cohort included patients who were (1) 65 years and older; (2) diagnosed with depression; (3) initiated SSRIs, SNRIs, or tetracyclics after a 6-month washout period; (4) continuously eligible for Medicare Part D at the 6-month baseline and during 1 year of follow-up; (5) noncomatose; and (6) not diagnosed with dementia in the baseline period.

Exposures and Outcome Definitions

The index antidepressant exposure was measured using Part D claims data. Antidepressant agents were grouped into SSRIs, SNRIs, and tetracyclics. These 3 classes were selected given their high prevalence of use in nursing home residents with depression.[30] SSRIs included sertraline, escitalopram, fluoxetine, fluvoxamine, citalopram, and paroxetine; SNRIs included venlafaxine, desvenlafaxine, milnacipran, and duloxetine; tetracyclics included mirtazapine and maprotiline (Appendix A). The National Drug Codes in the Part D claims were used to identify new users of 3 second-generation antidepressant classes.

The primary outcome—cognition—was identified using the MDS Cognition Scale. This is a 11-point scale that ranges from 0 (*intact cognition*) to 10 (*very severe impairment*) and evaluates short- and long-term memory, orientation, communication, and dressing.[36] The MDS Cognition Scale is highly correlated with the Mini-Mental State Examination in nursing home residents[37] and is a valid tool for measuring cognition in nursing home residents.[38] Cognition was measured as a continuous variable and at each quarterly assessment after antidepressant initiation until participants reached the end of the 1-year follow-up period. The following quarterly assessments were not included: patients who switched to a different antidepressant; those with a gap of more than 15 days in the use of the index antidepressant; or those who received psychotherapy.

Multiple Propensity Score Adjustment

Propensity scores are frequently applied in observational studies to reduce overt selection bias. Overt bias occurs as a result of existing pretreatment differences rather than treatment effects caused by lack of randomization in observational studies.[39] The propensity score is the conditional probability of assignment to a particular treatment group given a vector of observed covariates. The present study used the 7-step approach for the calculation of multiple propensity scores, as recommended by Spreeuwenberg et al.[40] These steps include estimating the treatment effects before propensity score adjustment, checking the distribution of the baseline covariates, selection of pretreatment characteristics to estimate the propensity scores, estimation of the propensity scores, checking distribution after propensity score adjustment, and estimating the treatment effect after propensity score adjustment. The baseline confounders and risk factors for the outcome were identified using the conceptual framework of the Andersen Behavioral Model. According to this model, an individual's health service use, including medication use, is a function of predisposing, enabling, and need factors.[41]

Predisposing, enabling, and need factors for this study were selected from past literature and based on their availability in the MDS and Medicare data sets.[9,42,43] Demographic characteristics such as age, gender, and race were grouped under predisposing factors. Enabling factors included type of prescription insurance. Need factors included cognitive characteristics, behavioral characteristics, comorbidities, and use of medications captured at the baseline period. Depression severity was captured using the MDS Depression Rating Scale. Cognitive characteristics were captured using the baseline MDS Cognition Scale. Behavioral characteristics were evaluated using Index of Social Engagement, Aggressive Behavior Scale, and Pain Scale.

Multiple propensity scores were calculated using the multinomial logistic regression model.[40] In the adjusted analysis, propensity scores along with their interaction terms were included to obtain robust estimates.[40] Calculation of multiple propensity scores using multinomial logistic regression required testing for the assumption of independence of irrelevant alternatives (IIAs).[44] The assumption was checked using the Hausman test by omitting SNRI as one of the treatment group. The Hausman test indicated that the IIA assumption was met (χ^2 test, 30.20; $P = 0.99$).

An appropriately calculated multiple propensity score should achieve balance in the distribution of all the observed covariates among the 3 treatment groups. Similarities among the 3 treatment groups before and after correction on the multiple propensity score were assessed using logistic regression analysis for the dichotomous variables, analysis of covariance for the continuous variables, and multinomial logistic regression analysis for the nominal variables.

Residents staying in the nursing home for long durations have their cognition measured repeatedly at every 90-day period between admission and annual assessment. Consequently, outcome measurements made on the same resident are correlated with each other. Thus, the repeated-measures mixedmodel analysis was used to examine the association between cognition and use of second-generation antidepressants. This regression model accounts for

correlation among outcome measurements collected on the same resident, allows for missing data, and uses all available data for the analysis.[45] Antidepressant treatment was used as a fixed factor along with 2 out of 3 propensity scores and their interactions terms as covariates.[40] Time was included as a covariate to account for any temporal trend in cognition scores, given that participants were followed for different amounts of time. The baseline MDS Cognition Scale score was included as a covariate, and the repeated-measures model only included quarterly cognition assessments after antidepressant initiation. The PROC MIXED in the SAS with REPEATED statement and AR (1) error-covariance structure was used to perform the repeated-measures mixed-model analysis, and results were presented as β estimates along with 95% CIs using SNRI use as the reference category. The parameter estimates provide the effect of second-generation antidepressants on repeated MDS Cognition Scale scores after controlling for baseline measure and other factors. A sensitivity analysis was conducted using the generalized linear regression model, where baseline covariates, including baseline MDS Cognition Scale score, were measured at admission assessment, and outcome was measured at the first quarterly assessment after the index antidepressant use to evaluate short-term cognitive effects.

Results

Figure 2 presents the process of development of the study cohort and sample selection. There were 1518 nursing home residents who met the inclusion and exclusion criteria. Of these, 1081 received SSRIs (71.21%), 320 received tetracyclics (21.08%), and the remaining 117 received SNRIs (7.71%). Table 1 presents baseline characteristics of SSRI, SNRI, and tetracyclic users before and after propensity score adjustment. After adjusting for propensity scores, there was no significant difference in any of the baseline characteristics except for age. Therefore, the multiple propensity score approach was able to achieve a balance for all the baseline characteristics.

Appendix B presents the distribution of propensity scores among the 3 treatment groups. The graph indicates that there is no common region of overlap across the 3 treatment groups, although multiple propensity scores were able to achieve a balance for all baseline characteristics that could have an effect on the final outcome. Hence, 2 types of adjusted regression analyses were conducted: Model 1 adjusted for propensity score, their interaction terms, and time, and Model 2 adjusted for demographic characteristics, behavioral characteristics, common chronic conditions and comedications, psychotherapy, and time.

Model 1 in Table 2 presents the results of propensity score–adjusted repeated-measures mixed model. When compared with SNRI users, there was no significant difference in MDS Cognition Scale score among the users of SSRIs (β = −0.14; 95% CI = −0.53, 0.25) or tetracyclics (β = −0.36; 95% CI = −0.80, 0.08). Similarly, covariates-adjusted repeated-measures mixed-model 2 did not find any significant difference in the MDS Cognition Scale score of SSRI users (β = −0.13; 95% CI = −0.41, 0.15) or tetracyclic users (β = −0.12; 95% CI = −0.43, 0.19) when compared with SNRI users (model 2 in Table 2). Consistent with the main findings, sensitivity analysis did not find any significant effect on first quarterly assessment of cognition after the index antidepressant use of SSRIs (β = −0.19; 95% CI =

−0.47, 0.10) or tetracyclics (β = −0.18; 95% CI = −0.50, 0.14) when compared with the SNRIs (Table 2).

Discussion

Per the authors' knowledge, this is the first population-based study to perform a head-to-head comparison of cognitive effects of the 3 most frequently used antidepressant classes in nursing home residents. This study did not find any significant effect of SSRIs or tetracyclics on cognition when compared with SNRIs. The similar cognitive effect of antidepressant classes could be attributed to similar effectiveness of second-generation antidepressants for depression.[13,14] Although SSRIs, SNRIs, and tetracyclics have different receptor-binding properties, which might lead to different onset of action and frequency of adverse events, the study findings suggest that these pharmacological differences do not translate into significant clinical differences with respect to cognition. Patients with dementia at baseline were excluded, and residents with depression had mild to moderate cognitive impairment at baseline. It is also possible that the MDS Cognition Scale may not be sensitive to the effects of 3 second-generation antidepressant classes on cognition.

The similar cognitive effect of antidepressant classes suggests that the effect on cognition is possibly a result of indirect effects via depression symptomatology, such as improving mood-related symptoms, rather than through direct pharmacodynamic effects mediated by neurophysiological changes in the brain. Further research is needed to understand the underlying mechanisms for cognition and long-term effectiveness of second-generation antidepressants. Although second-generation antidepressants have similar efficacy and effectiveness profiles for depression,[13,14] there are differences with respect to onset of action and adverse events. Therefore, physicians should recommend these second-generation antidepressants based on patients' physical and medical conditions as well as short- and long-term consequences of the treatment.

The main strength of this study lies in its design and analytical approach. The study used the propensity score approach to control for selection bias owing to nonrandomization of patients to the 3 treatment groups. Propensity scores were estimated using various observed pretreatment characteristics from the past literature. Histograms of propensity scores did not indicate sufficient region of overlap across the 3 treatment groups, suggesting that the propensity score–adjusted study design might not be well suited for head-to-head comparison of safety of 3 treatment groups regarding cognition. Results from Table 1 show that patients getting SSRIs, SNRIs, and tetracyclics are different from each other, which might have led to the lack of overlap in propensity score distributions across these 3 groups. However, propensity scores achieved balance for all the baseline characteristics that could have an effect on the final outcome. Thus, estimated propensity scores were used as covariates in the repeated-measures mixed model to adjust for any differences that were present among the treatment groups on pretreatment characteristics. The interaction terms between the 2 propensity scores were included to achieve robust estimates.[40] Additional repeated-measures mixed-model analysis was conducted using baseline characteristics as control variables in the analysis looking at the association between cognition and 3 second-generation antidepressant classes. This study used a 1-year follow-up period. Treatment

periods and follow-up intervals frequently used in clinical trials have varied from 1 to 3 months, but a longer duration helped to investigate to what extent duration of antidepressant therapy predicts neurocognitive outcome. Finally, only new users of second-generation antidepressants were included in the present study to address the issue of prevalence bias.[46]

The findings of this study should be interpreted in light of some limitations. The 3 treatment groups were imbalanced, which might affect the study results. Use of second-generation antidepressants was ascertained using pharmacy claims. Medications as a component of Part A bundled payments for short, postacute nursing home stays may not have been captured. However, patients using any antidepressant according to MDS records at the baseline cognitive assessment were excluded from the analysis, which enabled comparison of the cognitive changes among new users of second-generation antidepressant classes, at least among those who continued the second-generation antidepressant until the next quarterly assessment. The claims capture only dispensing data and not actual use by patients. Additionally, concomitant medications that can have effects on cognition were not analyzed. However, use of comedications at baseline was treated as one of the control variables to control for comedication use in the adjusted analysis. The present study used Medicare data, which is a secondary database and thus has limitations arising from miscoding and undercoding.[47] All the diseases and outcome measures were ascertained using data available in MDS. These data are submitted by the health care providers. Incomplete, inaccurate, and erroneous information submitted by the health care providers and availability of insufficient clinical detail in the ICD-9-CM system may limit the accuracy of administrative data.[48] Depressed patients often do not fully recover cognitively after a major depressive episode, and neurocognitive rest-symptoms may represent depressive rest-symptomatology or other factors coexistent with depression and may not necessarily be a sign of adverse medication effects. It is possible that the propensity score model may not completely control for hidden nonobservable covariates that may alter the estimation and interpretation of study findings, particularly because there remained 2 distinct population distributions for propensity scores by antidepressant agents. However, results of sensitivity analysis confirmed the study findings. Finally, the study population comprised elderly nursing home residents, and hence, study findings may not be generalizable to other treatment settings.

Conclusions

The cognitive effects of SSRIs, SNRIs, and tetracyclics were similar in the elderly nursing home residents with depression. The findings remained consistent across multiple statistical models and sensitivity analysis. Although the second-generation antidepressant classes differ in their onset of action and frequency of adverse events; these pharmacological differences among second-generation antidepressants do not translate into significant clinical differences in cognitive status in elderly patients in the nursing home setting. Further studies are needed to evaluate the long-term cognitive effects of the second-generation antidepressants in nursing home residents, a setting where patients are at high risk for depression and cognitive impairment.

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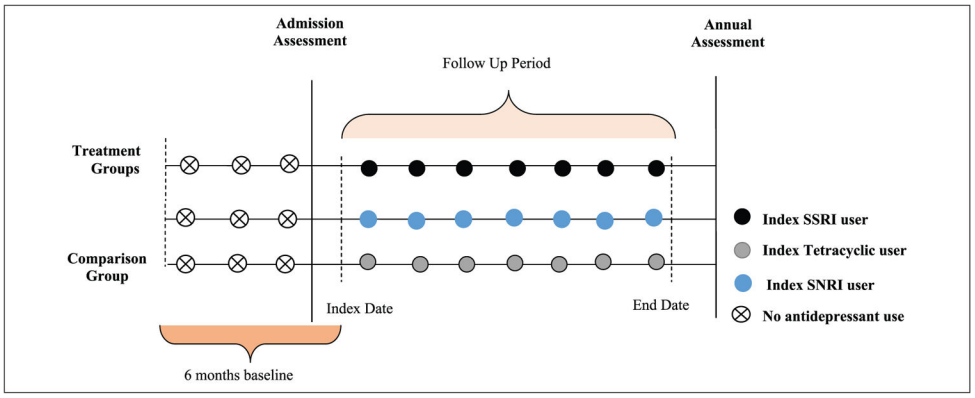


Figure 1.

Development of Study and Comparison Groups.

Abbreviations: SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin-norepinephrine reuptake inhibitors.

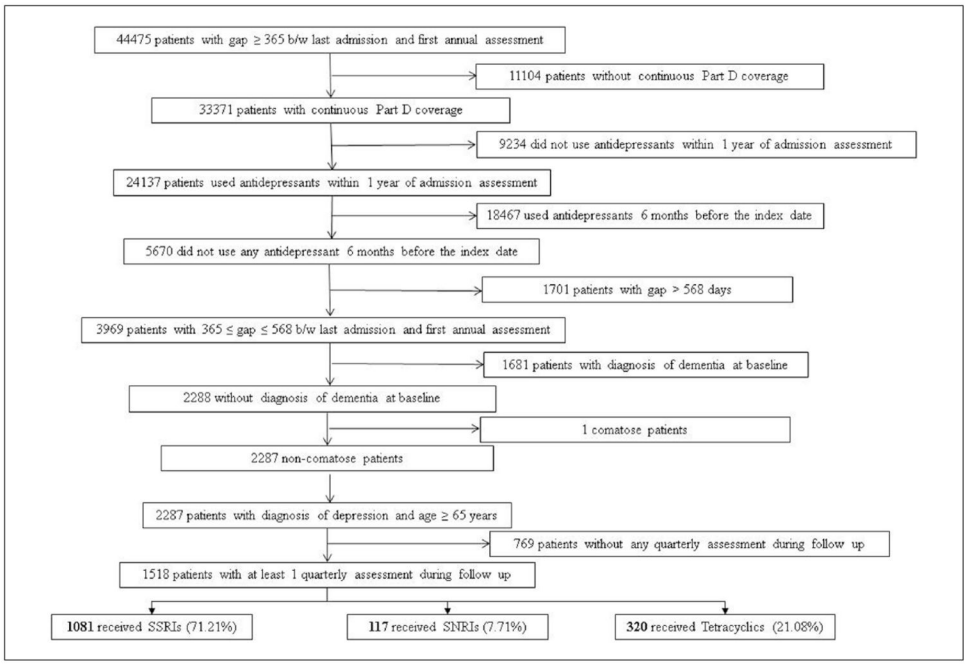
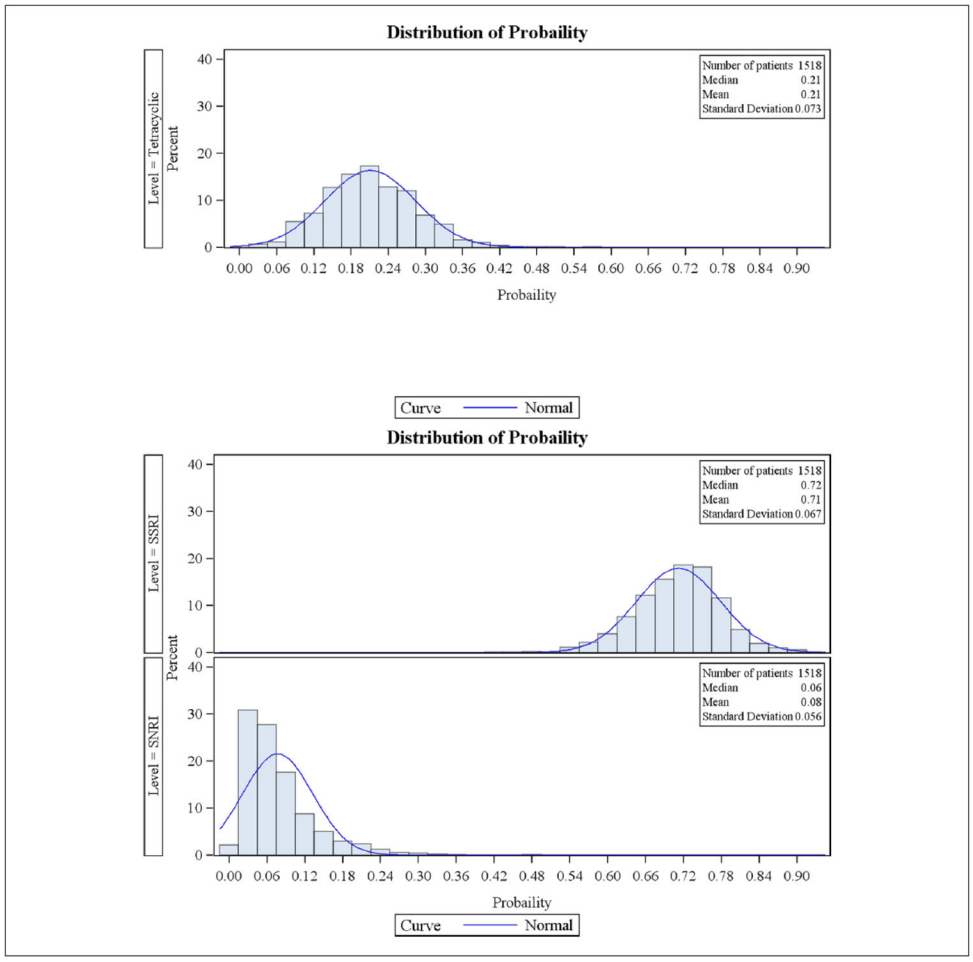


Figure 2.

Flowchart of Study Sample Selection and Cohort Development.

Abbreviations: SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor.



Appendix B.

Distribution of Propensity Scores Across the Users of Second-generation Antidepressants. Abbreviations: SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin-norepinephrine reuptake inhibitors.

Table 1

Baseline Characteristics of Elderly Nursing Home Patients With Depression Using Second-Generation Antidepressants.

	SSRI Users (n = 1081)	SNRI Users (n = 117)	Tetracyclic Users (n = 320)	*P* Value Before Adjustment	*P* Value After Adjustment
Demographic characteristics					
Gender (%)				0.017[a]	0.190
Female	70	38	24		
Male	30	62	76		
Age in years, mean (SD)	80.55 (9.82)	77.64 (9.05)	82.32 (8.73)	<0.0001[a]	0.021[a]
Race (%)				0.153	0.355
White	78	70	75		
Nonwhite	13	15	14		
Missing	8	14	11		
Behavioral characteristics, mean (SD)					
Baseline MDS Cognition Scale	2.47 (2.37)	2.31 (2.23)	2.71 (2.48)	0.179	0.161
Index of Social Engagement	2.48 (1.50)	2.79 (1.57)	2.40 (1.46)	0.048[a]	0.888
Depression Rating Scale	0.85 (1.53)	0.91 (1.60)	0.73 (1.26)	0.349	0.332
Aggressive Behavior Scale	0.29 (0.94)	0.28 (0.90)	0.26 (0.82)	0.869	0.857
Pain scale	0.73 (0.75)	0.96 (0.82)	0.68 (0.74)	0.003[a]	0.788
Medical characteristics (%)					
Arthritis	29	32	30	0.820	0.907
Diabetes	38	47	32	0.011[a]	0.120
Hypertension	74	71	76	0.611	0.931
Cancer	6	3	8	0.287	0.897
Stroke	22	20	25	0.467	0.769
Congestive heart failure	22	29	22	0.206	0.875
Chronic obstructive pulmonary disease	20	29	20	0.058	0.731
Parkinson	4	5	4	0.636	0.783
Other cardiac disorders	23	28	19	0.140	0.599
Schizophrenia	4	6	2	0.063	0.215
Anxiety disorder	15	15	14	0.947	0.941

	SSRI Users (n = 1081)	SNRI Users (n = 117)	Tetracyclic Users (n = 320)	*P* Value Before Adjustment	*P* Value After Adjustment
Asthma	4	2	3	0.278	0.661
Manic depression	2	2	1	0.316	0.415
Medication characteristics (%)					
Antipsychotics	11	12	9	0.569	0.622
Antianxiety	18	19	14	0.174	0.164
Hypnotics	11	14	12	0.633	0.872
Diuretics	37	37	30	0.123	0.093
Use of psychotherapy	1	1	2	0.813	0.962

Abbreviations: SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; MDS, Minimum Data Set.

[a] *P* value significant at 0.05.

Table 2

Repeated-Measures Mixed Model for the Association Between Second-Generation Antidepressants and Cognition.

	Parameter Estimate	95% CI	*P* Value
Model 1: multiple propensity score-adjusted repeated-measures mixed model[a]			
SNRIs	1.00	Reference	
SSRIs	−0.14	−0.53, 0.25	0.471
Tetracyclics	−0.36	−0.80, 0.08	0.112
Model 2: adjusted repeated-measures mixed model[b]			
SNRIs	1.00	Reference	
SSRIs	−0.13	−0.41, 0.15	0.360
Tetracyclics	−0.12	−0.43, 0.19	0.463
Sensitivity analysis: generalized linear regression model			
SNRIs	1.00	Reference	
SSRIs	−0.19	−0.47, 0.10	0.205
Tetracyclics	−0.18	−0.50, 0.14	0.281

Abbreviations: CI, confidence interval; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin-norepinephrine reuptake inhibitors; MDS, Minimum Data Set.

[a]Model adjusted for propensity score and their interaction terms, and time.

[b]Model adjusted for the following covariates and time: demographic characteristics such as age, gender, race; behavioral characteristics such as baseline

MDS Cognition Scale, Index of Social Engagement, Depression Rating Scale, Aggressive Behavior Scale, Pain Scale; common chronic conditions such as arthritis, cancer, asthma, chronic obstructive pulmonary disease, Parkinson's, diabetes, hypertension, stroke, congestive heart failure, other cardiac disorders, schizophrenia, anxiety disorder, manic depression; and use of medications such as antipsychotics, antianxiety medications, hypnotics, diuretics; and use of psychotherapy.

Appendix A

List of Second-Generation Antidepressants Used in the Study

Drug Class	Medications
SSRIs	Sertraline, escitalopram, fluoxetine, fluvoxamine, citalopram, and paroxetine
SNRIs	Venlafaxine, desvenlafaxine, milnacipran, and duloxetine
Tetracyclics	Mirtazapine and maprotiline

Abbreviations: SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin-norepinephrine reuptake inhibitors.