Potential Underuse, Overuse, and Inappropriate Use of Antidepressants in Older Veteran Nursing Home Residents

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OBJECTIVES: To examine prevalence and resident- and site-level factors associated with potential underuse, overuse, and inappropriate use of antidepressants in older Veterans Affairs (VA) Community Living Center (CLC) residents.

DESIGN: Longitudinal study.

SETTING: One hundred thirty-three VA CLCs.

PARTICIPANTS: Three thousand six hundred ninety-two veterans aged 65 and older admitted between January 1, 2004, and June 3, 2005, with long stays (≥90 days).

MEASUREMENTS: Prevalence of potential underuse, inappropriate use, and overuse of antidepressants in residents with and without depression (as documented according to *International Classification of Diseases, Ninth Revision*, Clinical Modification, codes or Depression Rating Scale).

RESULTS: Selective serotonin reuptake inhibitors were the most commonly prescribed antidepressant. Of the 877 residents with depression, 25.4% did not receive an antidepressant, suggesting potential underuse. Of residents with depression who received antidepressants, 57.5% had potential inappropriate use due primarily to problems seen with drug–drug and drug–disease interactions. Of the 2,815 residents who did not have depression, 1,190 (42.3%) were prescribed one or more antidepressants; only 48 (4.0%) of these had a Food and Drug Administration–approved labeled indication, suggesting potential overuse. Overall, only 17.6% of antidepressant use was appropriate (324/1,844). The only consistent resident factor associated with potential underuse and overuse use was taking an antipsychotic without evidence of schizophrenia (underuse: adjusted relative risk ratio (ARRR) = 0.56, 95% confidence interval (CI) = 0.33–0.94; overuse: adjusted odds ratio = 1.52, 95% CI = 1.21–1.91). Having moderate to severe pain (ARRR = 1.54, 95% CI = 1.08–2.20) and the prescribing of an anxiolytic or hypnotic (ARRR = 1.33, 95% CI = 1.02–1.74) increased the risk of potential inappropriate antidepressant use.

CONCLUSION: Potential problems with the use of antidepressants were frequently observed in older U.S. veteran CLC residents. Future studies are needed to examine the true risks and benefits of antidepressant use in CLC and non-VA nursing homes. **J Am Geriatr Soc 59:1412–1420, 2011.**

Key words: aged; nursing homes; depression; pharmacoepidemiology

Depression is common in older nursing home residents.[1] One seminal study reported a 12% prevalence rate for major depression using the American Psychiatric Association *Diagnostic and Statistical Manual of Psychiatric Disorders, Third Edition, Revised* (DSM-III-R) criteria in older residents in a 1,100-bed nursing home.[2,3] Minor, subsyndromal, or subthreshold depression was seen in an additional 30% of these older nursing home residents.[3] In contrast, a more-recent national study of nursing homes found that only 20% of older residents had a diagnosis of

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depression indicated in their quarterly Minimum Data Set (MDS) assessment.[4] Depression is important to treat in older nursing home residents and is commonly associated with morbidity (e.g., hospitalization, functional status decline) and mortality.[1]

Depression in nursing homes can be treated with one or a combination of the following modes of treatment: electroconvulsive therapy, psychological or psychiatric intervention, and antidepressant therapy.[1] Antidepressant therapy is the most common treatment in nursing home residents.[1] Moreover, the prevalence of antidepressant use in U.S. nursing home residents has more than doubled—from 21.9% in 1996 to 47.5% in 2006.[5] This prevalence rate of 47.5% is consistent with the national rate of antidepressant use in Veterans Affairs (VA) Community Living Centers (CLCs).[6] Despite these high rates, data are conflicting regarding possible undertreatment of depression in nursing home residents. Recent national information shows that fewer than 5% of nursing home residents with symptoms of depression determined through the quarterly MDS assessments were not treated with an antidepressant.[7] In contrast, a 2000 study of Ohio nursing home residents found that 23% of those with a depression diagnosis did not receive an antidepressant.[8] Concomitantly, there is limited information that suggests that potential overuse and inappropriate use of antidepressants may be problematic in older nursing home residents.[9,10] Given this background, the objectives of this study were to estimate the prevalence and resident- and site-level factors associated with potential underuse, inappropriate use, and overuse of antidepressants in older VA CLC residents.

METHODS

Study Design, Setting, Data Sources, and Sample

This was a longitudinal study of 3,692 long-stay (≥90 days) residents aged 65 and older admitted to any one of the 133 VA CLCs located in the United States between January 1, 2004, and June 30, 2005. The mission of these CLCs (previously called Nursing Home Care Units) is to provide compassionate care to eligible veterans with sufficient functional impairment to require this level of service. Veterans with chronic stable conditions, including dementia, those requiring rehabilitation or short-term specialized services such as respite or intravenous therapy, and those who need inpatient hospice, can receive this type of care in VA CLCs. These CLCs are located in 21 regions across the United States called Veterans Integrated Services Networks (VISNs). The development of a merged database that included Minimum Data Set (MDS) and medication dispensing information from the Pharmacy Benefits Management Services (PBM) used for this study was recently described.[6] Briefly, CLC staff evaluated all veterans receiving care in a VA CLC using the MDS version 2.0. MDS 2.0 is a reliable standardized tool to identify the functional, psychological, and health status needs of residents and to evaluate the quality of care that these residents are receiving.[11] All MDS data were collected through resident interviews, staff interviews, and reviews of medical records. For all CLC residents, the MDS was completed at admission (within 14 days of admission), quarterly thereafter (within 90 days of previous evaluation), and at the time of any significant change in status (e.g., major change in cognitive function or functional status decline). The VA PBM provided all prescription data for the defined study cohort. These data included the start date, drug name, drug strength, dosage form, directions for use, VA therapeutic class, and amount of each drug dispensed. *International Classification of Diseases, Ninth Revision*, Clinical Modification (ICD-9-CM) codes for inpatient and outpatient diagnoses in the previous year from the VA National Patient Care Database (NPCD) records were also linked to the merged database mentioned previously. This final merged database, which was prepared using encrypted identifiers that were consistent across the three individual databases, was used to conduct the present analyses.

The sample was first stratified according to depression status determined according to ICD-9 codes. Specifically, any hospitalization or outpatient visit to a VA in the previous year during with depression was addressed was identified and noted using ICD-9-CM codes (296.2, 296.3, 298.0x, 300.4x, 309.1x, 311.xx, 301.12, 309.0x).[12,13] This approach was chosen because it was used in two previous VA studies examining the quality of depression care in outpatients and because a previous study using ICD-9 codes to identify depression found acceptable specificity (88%) but lower sensitivity (52%).[12–14] Thus, although this approach may underestimate the "true rate" of depression, it is likely to be more accurate than using just the listing of depression on a resident's problem list or in Section I of the MDS, entitled "Disease Diagnoses."[11] To ensure that those who did not have VA health service utilization in the previous year were not misclassified and to improve sensitivity, those with a high likelihood of depression on admission (MDS Depression Rating Scale (DRS) score >3)[15] were also included. The DRS is a summary of seven symptoms detected by nursing home staff that capture verbal and nonverbal indicators of depressed mood and has been shown to be a reliable (sensitivity, 91% and specificity, 69% with a psychiatrist diagnosis) and valid measure of depression in nursing home residents.[15] Eight hundred seventy-seven residents were included in the depression sample (796 according to ICD-9 codes and 181 according to DRS >3 only); the remaining 2,815 had no documented depression. The Pittsburgh VA institutional review board and research and development committees approved this study.

Main Outcome Measures

Antidepressants on the VA national formulary in 2004/05 (VA Classes CN601, CN609, CN802) included those in the following four discrete groups: tricyclic antidepressants (TCAs; amitriptyline, desipramine, doxepin, nortriptyline), selective serotonin reuptake inhibitors (SSRIs; paroxetine, sertraline, fluoxetine, citalopram), serotonin-norepinephrine reuptake inhibitors (SNRIs; venlafaxine), and other antidepressants (trazodone, mirtazapine, methylphenidate, bupropion). Methylphenidate was included because it is frequently used to treat depression in older adults.

To operationally define potential underuse and inappropriate use of antidepressants in the depression group, two specific authoritative sources were consulted: a guideline from the American Medical Directors Association (AMDA) and quality-of-care indicators from the Centers

for Medicare and Medicaid Services (CMS) for appropriate use of antidepressants for treating depression in nursing homes.[16,17] The Veterans Health Administration and Department of Defense (VHA/DOD) guideline for treating adults with depression and another from England that focused on treating older adults with depression in the primary care setting were also used.[18,19] Using a previously published and validated approach, explicit criteria for potentially inappropriate use were created that an expert panel consisting of a nurse pharmacoepidemiology researcher (MJP), a geriatric clinical pharmacist (TPS), two geriatricians (SMH, DRB), and a geriatric psychiatrist–psychopharmacologist (MWD) reviewed, edited, and agreed upon.[20] Potential inappropriate use in those in the depression group was ascertained by applying these explicit criteria to determine whether there were one or more problems in five specific quality areas: selection (e.g., choosing an antidepressant such as amitriptyline that has anticholinergic or orthostatic effects), maintenance dosage exceeding or below minimum effective dosage (e.g., highest daily dose during the 90-day period to account for the time needed to "start low and go slow" or titrate new antidepressants), clinically important drug–drug interactions; clinically important drug–disease interactions, and therapeutic duplication (use of $\geq$2 TCAs, SSRIs, or SNRIs concomitantly) (Appendix I). The lack of an order for an antidepressant during the 90-day follow-up period indicated potential underuse in the group with depression. The rationale for this operational definition is that many experts recommend antidepressant treatment for a period of time ranging from 1 to 3 years to reduce the likelihood of major depression reoccurrence and relapse in older residents with depression.[17,18] All persons in the group with depression taking an antidepressant that was not considered potentially inappropriate were included in the appropriate use category.

To operationally define potential overuse in those without depression, two specific authoritative sources were consulted: a joint statement of the members of the Long Term Care Professional Leadership Council (LTCPLC) and the Food and Drug Administration (FDA) Web site.[21,22] Potential overuse of antidepressant use in residents without depression was operationally defined as lack of a FDA-approved labeled indication. (See footnote of Table 2 for further details.)[21,22] ICD-9 codes were used to determine these indications using previously established methods.[23] Appropriate use of antidepressants in participants without depression was defined as any use not deemed to be overuse.

Independent Variables

Based on previous literature, the independent variables included demographic characteristics, health status factors, and psychiatric or neurological problems.[10,23,24] Using data from the admission MDS, categorical variables were created for age (65–74, 75–84, $\geq$85), race (black, white, or other), sex (male or female), and educational level (<high school, high school, >high school).

Regarding health status factors, a continuous variable for activity of daily living (ADL) dependencies was created from the admission MDS that had a range from 0 to 20 points and identified the amount of assistance needed from staff for five activities (bathing, dressing, grooming, toileting, and eating).[25] A continuous variable was created for the Charlson Comorbidity Index based on the methods of Deyo, which creates a score (range 0–34) calculated based on the presence of 18 chronic conditions documented in the electronic medical record using ICD-9 codes.[26,27] The number of prescribed drugs at admission was also quantified (excluding those specified below), and a dichotomous variable for physical restraint use was created as noted on the MDS. In addition, dichotomous variables for individual conditions noted on the admission MDS were examined (cancer, chronic obstructive pulmonary disease, diabetes mellitus, arteriosclerotic heart disease, arthritis, hip fracture history, hypertension, and osteoporosis).

Psychiatric and neurological problem variables were created using ICD-9 codes from VA hospitalizations or outpatient visits in the previous year. Specifically, dichotomous variables were created for cerebrovascular accident (CVA); seizure disorder; Parkinson's disease; any neuropathic pain; bipolar disease; posttraumatic stress disorder (PTSD); other anxiety disorder; and Alzheimer's, vascular, or other dementia.[27] Data from the admission MDS evaluation were also used to create a dichotomous variable for behavioral problems and moderate to severe pain and a categorical variable for cognitive function (Cognitive Performance Score (CPS): intact, mild to moderate, severe).[28,29] Finally, from PBM data, a dichotomous variable was created denoting use of individual medication classes (antipsychotics (CN701 and 709) in residents without schizophrenia, anxiolytics and hypnotics (CN302 and 309), acetylcholinesterase inhibitors (ACHEIs) and memantine (CN900)). Two dichotomous variables (bed size and geographic region) were also included to control for potentially confounding site factors.[5]

Statistical Analyses

Descriptive statistics were used to summarize independent variables and study outcomes. To include the approximately 3% of residents with missing data on education or cognitive performance status in the analyses, dummy variables were created for a "missing" category. The number and percentage of residents who were prescribed individual classes of antidepressants (TCAs, SSRIs, SNRIs, other) was described. In those with depression, the number and percentage of residents with specific types of potentially inappropriate antidepressant use were also described. A multinomial regression analysis was conducted to identify resident factors associated with underuse or inappropriate use versus appropriate use (reference group) of antidepressants in residents with depression. A backward selection approach (alpha = 0.10) was used to identify health status factors and psychiatric and neurological conditions to be added to the demographic characteristics and resident site factors in the final models. Estimated adjusted relative risk ratios (RRRs) and 95% confidence intervals (CIs) adjusted for clustering according to CLC are reported. Multiparameter Wald tests quantified the association between each outcome and the categorical variables with more than two levels. A multivariable logistic regression analysis in residents without depression was also conducted by first removing from the sample those with a FDA-approved labeled indication ("appropriate use") and the overuse

group was compared with those with no use of antidepressants.[30] Statistical analyses were performed using SAS, version 9 (SAS Institute, Inc., Cary, NC) and Stata (StataCorp, College Station, TX).

RESULTS

Table 1 compares the characteristics of CLC residents who were depressed (n = 877) with the characteristics of those who were not (n = 2,815). The groups were similar with regard to most characteristics. White residents and those with more comorbidities were more likely to be depressed than not. Those who were not depressed had more ADL dependencies and more-severe cognitive impairment than those who were depressed. The most common medication class that those without schizophrenia in both groups were taking was antipsychotics.

Table 2 summarizes antidepressant use overall and according to specific classes for residents with and without depression. The most common antidepressant class used by both groups was SSRIs. No use of monoamine oxidase inhibitors (MAOIs) was documented. Of the 877 residents with depression, 74.6% (n = 654) took an antidepressant, which suggests potential underuse in 25.4% (n = 223) of these residents. Of residents without depression, 42.3% took an antidepressant, which suggests potential overuse, because only 48 of these 1,190 taking an antidepressant had evidence of a FDA-approved labeled indication. Thus, only 4.0% of antidepressant use in those without depression was appropriate.

Table 3 summarizes potential inappropriate drug use in residents with depression. Nearly six in 10 residents with depression (n = 378) who received an antidepressant had one or more prescribing problems. Thus, appropriate antidepressant use was seen in 276 of 654 (42.5%). Drug–drug and drug–disease interactions were the most common problems, whereas therapeutic duplication and selection were the least frequent prescribing problems. By combining appropriate use regardless of depression group (48+276/1,190+654 = 17.6%), fewer than two in 10 antidepressant prescriptions were not problematic.

Table 4 summarizes the results of the multivariable multinomial logistic regression models for potential underuse and inappropriate use of antidepressant versus appropriate use in those who were depressed. Factors significantly associated with a lower risk of potential underuse in residents with depression included polypharmacy (taking >5 medications), having a history of cancer, and taking an antipsychotic without evidence of schizophrenia; the only factor associated with a greater risk of potential underuse was having ADL dependencies. Regarding potential inappropriate use, black residents and residents with cancer were significantly less likely to have this problem. Residents with moderate to severe pain and those taking an anxiolytic or hypnotic were at significantly greater risk of inappropriate use than appropriate use.

Table 5 summarizes the results of the multivariable logistic regression models for potential overuse versus no antidepressant use in residents who were not depressed. Residents aged 85 and older had a significantly lower risk of overuse, and the risk of overuse decreased with increasing comorbidity index score. Overuse was significantly more

Table 1. Patient and Facility Characteristics for Older Veterans with and without Depression in Community Living Centers

Characteristic	Depressed (n = 877)	Not Depressed (n = 2,815)
Demographic, n (%)		
Age		
65–74	265 (30.2)	869 (30.9)
75–84	468 (53.4)	1,458 (51.8)
≥85	144 (16.4)	488 (17.3)
Race		
White	760 (86.7)	2,221 (78.9)
Black	87 (9.9)	412 (14.6)
Other	30 (3.4)	182 (6.5)
Female	37 (4.2)	66 (2.3)
Education		
<High school	253 (28.8)	859 (30.5)
High school	404 (46.1)	1,312 (47.7)
>High school	208 (23.7)	614 (21.8)
Not assessed	12 (1.37)	30 (1.07)
Health status		
Number of activities of daily living dependent in, mean ± SD	8.6 (6.3)	9.3 (6.5)
Comorbidity index, mean ± SD	2.9 (2.3)	2.6 (2.2)
Number of medications other than antidepressant, n (%)		
0–5	243 (27.7)	744 (26.4)
6–10	258 (29.4)	786 (27.9)
11–15	158 (18.0)	587 (20.8)
≥16	218 (24.9)	698 (24.8)
Comorbidities, n (%)		
Chronic obstructive pulmonary disease	259 (29.5)	747 (26.5)
Diabetes mellitus	309 (35.2)	1,077 (38.3)
Cancer	162(18.5)	472 (16.8)
Arthritis	255(29.1)	756 (26.9)
Arteriosclerotic heart disease	233 (26.6)	656 (23.3)
Hip fracture	43 (4.9)	144 (5.1)
Hypertension	588 (67.0)	1,879 (66.7)
Osteoporosis	58 (6.6)	160 (5.68)
Neurological or psychiatric problems, n (%)		
Cerebrovascular accident	152 (17.3)	507 (18.0)
Seizure disorder	52 (5.9)	146 (5.19)
Parkinson's disease	80 (9.1)	146 (5.19)
Any neuropathic pain	266 (30.3)	609 (21.6)
Bipolar disease	22 (2.5)	64 (2.3)
Schizophrenia	86 (9.8)	283 (10.0)
Posttraumatic stress disorder	124 (14.1)	121 (4.3)
Other anxiety	148 (16.9)	133 (4.7)
Alzheimer's disease	106 (12.1)	286 (10.2)
Vascular dementia	89 (10.1)	150 (5.3)
Other dementia	336 (38.3)	753 (26.7)
Behavior problem	171 (19.5)	347 (12.3)
Moderate to severe pain	223 (25.4)	645 (22.9)
Cognitive function		
Intact	442 (50.4)	1,497 (53.2)
Mild to moderate impairment	325 (37.1)	880 (31.3)

(*Continued*)

Table 1. (Contd.)

Characteristic	Depressed (n = 877)	Not Depressed (n = 2,815)
Severe impairment	90 (10.3)	384 (13.6)
Not assessed	20 (2.3)	54 (1.9)
Use of antipsychotic in those without schizophrenia	214 (24.4)	512 (18.2)
Use of anxiolytic or hypnotic	68 (7.7)	163 (5.8)
Use of acetylcholinesterase inhibitor	156 (17.8)	363 (12.9)
Use of memantine	35 (4.0)	78 (2.8)
Site level indicators, n (%)		
Bed size		
Small (<60)	126 (14.4)	384 (13.6)
Medium (60–119)	416 (47.4)	1,328 (47.2)
Large (≥120)	335 (38.2)	488 (39.2)
Region		
Northeast	221 (25.2)	695 (24.7)
Midwest	191 (21.8)	556 (19.7)
South	331 (37.7)	1,158 (41.1)
West	134 (15.3)	406 (14.4)

SD = standard deviation.

likely in those with mild to moderate cognitive impairment, polypharmacy (taking >5 medications), CVA, other anxiety, and taking an antipsychotic without evidence of schizophrenia.

Table 2. Antidepressant Medication Use in Veteran Community Living Center Residents with and without Depression

Variable	n (%)	
	Depressed (n = 877)	Not Depressed (n = 2,815)
Any antidepressant use	654 (74.6)*	1,190 (42.3)†
Antidepressant class use*		
Selective serotonin reuptake inhibitor	494 (56.4)	754 (26.8)
Serotonin–norepinephrine reuptake inhibitor	44 (5.0)	42 (1.5)
Tricyclic antidepressant	32 (3.7)	87 (3.1)
Other	290 (33.1)	546 (19.4)

* Use of specific classes sums to greater than 74.6% because some patients took more than one agent concomitantly.

† Only 48 of 1,190 (4.0%) residents receiving an antidepressants had a Food and Drug Administration–approved labeled indication (venlafaxine for panic disorder, generalized anxiety disorder, and social phobia; doxepin for moderate pruritus due to atopic dermatitis or lichen simplex chronicus; bupropion for smoking cessation; methylphenidate for narcolepsy or attention deficit disorder; escitalopram for generalized anxiety disorder; fluvoxamine for social phobia or obsessive compulsive disorder; fluoxetine for obsessive compulsive disorder or panic disorder; duloxetine for diabetic peripheral neuropathy; paroxetine for generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, or social phobia; sertraline for obsessive compulsive disorder, panic disorder, or posttraumatic stress disorder.

Table 3. Potentially Inappropriate Antidepressant Use in Residents with Depression According to Type of Problem and Overall (n = 877)

Type of Problem*	n (%)	Most Common Drugs Involved (n)
Selection	32 (3.7)	Amitriptyline (12)
		Nortriptyline (11)
		Doxepin (7)
Dosage	77 (8.8)	Trazodone (28)
		Sertraline (16)
		Venlafaxine (10)
Drug–drug interaction	227 (25.9)	SSRI and trazodone (73)
		Fluoxetine or paroxetine and metoprolol (41)
		Mirtazapine and SSRI (15)
Drug–disease interaction	223 (25.4)	SSRI and falls (73)
		Venlafaxine and hypertension (22)
		Tricyclic antidepressant and constipation (8)
Therapeutic	10 (1.1)	SSRI and SSRI (10)
Duplication		
Any problem	378 (43.1)	

* Sums to more than 43.1% because some residents had more than one type of problem.

SSRI = selective serotonin reuptake inhibitor.

DISCUSSION

In this study, nearly 50% of all older long-stay veteran nursing home residents received an antidepressant, which is consistent with the rate of nearly 48% of non-VA nursing home residents taking an antidepressant.[6] That depression was found in nearly 25% of residents is also consistent with previously published studies,[3,10] although it was found that nearly 25% of those with depression did not receive an antidepressant, suggesting potential underuse. This rate is considerably less than the 45% of nursing home residents with MDS-reported depression who were not being given an antidepressant in a multistate U.S. sample,[10] but it is consistent with the rates from more-recent studies that show that between 21% and 34% of nursing home residents with depression do not receive an antidepressant.[8,31] The multivariable analyses of factors associated with underuse of antidepressants suggest that prescribers may be more cautious in residents with greater ADL dependencies. This may reflect appropriate concern that the likelihood of antidepressant adverse effects is greater than the potential benefits in these vulnerable people. It is hoped that better detection and monitoring of depression using the valid, reliable, and frequently used nine-item Patient Health Questionnaire, which is replacing the DRS in MDS version 3.0 and is scheduled to be implemented in non-VA nursing homes in the fall of 2010 and VA CLCs in 2011, will further reduce the rate of antidepressant underuse.[32]

Of persons who were depressed and receiving an antidepressant, nearly 60% had evidence of potentially inappropriate use, with one or more prescribing problems. The least-frequent problems were therapeutic duplication and selection. Medication selection was potentially

Table 4. Comparison of Factors Associated with Underuse (n = 223) and Inappropriate Use (n = 378) and Those Associated with Appropriate Use (Reference Group; n = 276) of Antidepressants in Residents with Depression

Factor	Adjusted Relative Risk Ratio (95% Confidence Interval)	
	Underuse (n = 223)	Inappropriate Use (n = 378)
Demographic		
Age (reference 65–74)		
75–84	0.90 (0.59–1.39)	1.27 (0.87–1.84)
≥85	0.92 (0.52–1.62)	1.29 (0.79–2.11)
Race (reference white)		
Black	0.85 (0.49–1.49)	0.48 (0.30–0.76)*
Other	1.21 (0.48–3.01)	0.86 (0.33–2.25)
Female gender	1.55 (0.68–3.53)	0.67 (0.28–1.61)
Education (reference <high school)		
High school	0.84 (0.55–1.28)	0.89 (0.59–1.33)
>High school	1.02 (0.58–1.79)	0.90 (0.57–1.44)
Not assessed	1.15 (0.27–4.81)	1.23 (0.26–5.83)
Health status		
Activity of daily living score (per unit increase)	1.05 (1.02–1.09)*	1.02 (0.99–1.04)
Number of medications other than antidepressant (reference 0–5)		
6–10	0.57 (0.36–0.91)*	1.39 (0.88–2.19)
11–15	0.40 (0.23–0.73)*	1.58 (0.94–2.66)
≥16	0.46 (0.28–0.76)*	1.79 (1.09–2.94)
Cancer	0.52 (0.33–0.81)*	0.62 (0.41–0.94)*
Neurological or psychiatric problem		
Cerebrovascular accident	0.63 (0.37–1.08)	1.33 (0.83–2.15)
Behavior problem	1.51 (0.91–2.49)	0.69 (0.44–1.08)
Moderate to severe pain	0.79 (0.51–1.21)	1.54 (1.08–2.20)*
Use of anxiolytic or hypnotic	1.08 (0.81–1.44)	1.33 (1.02–1.74)*
Use of antipsychotic in resident without schizophrenia	0.56 (0.33–0.94)*	0.90 (0.62–1.30)
Site-level indicators		
Bed size (reference small (<60))		
Medium (60–120)	0.90 (0.49–1.66)	0.97 (0.56–1.66)
Large (>120)	0.59 (0.32–1.11)	1.01 (0.60–1.71)
Region (reference Northeast)		
Midwest	0.76 (0.44–1.29)	0.78 (0.47–1.31)
South	0.61 (0.38–0.99)	1.03 (0.66–1.60)
West	0.77 (0.43–1.37)	1.28 (0.74–2.19)

* $P < 0.05$; for categorical variables, contrasts are noted as being statistically significant only when the overall effect in the equation is significant.
Wald chi-square (46) = 147.57; probability > chi-square = 0.0000; log pseudolikelihood = −871.022; pseudo coefficient of determination = 0.076.

Table 5. Comparison of Factors Associated with Overuse (n = 1,142) and No Use (Reference Group; n = 1,625) in Residents without Depression*

Factor	Adjusted Odds Ratio (95% Confidence Interval)
Demographic	
Age (reference 65–74)	
75–84	0.89 (0.73–1.09)
85+	0.70 (0.57–0.87)†
Race (reference white)	
Black	0.82 (0.65–1.03)
Other	0.69 (0.40–1.19)
Female	1.28 (0.81–2.01)
Education (reference <high school)	
High school	1.08 (0.88–1.33)
>High school	1.32 (1.05–1.68)
Not assessed	0.63 (0.27–1.43)
Health status	
Comorbidity index	0.92 (0.88–0.96)†
Number of medications other than antidepressant (reference 0–5)	
6–10	1.88 (1.48–2.38)†
11–15	2.50 (1.93–3.24)†
≥16	3.50 (2.79–4.38)†
Cancer	1.27 (0.99–1.63)
Chronic obstructive pulmonary disease	1.21 (1.00–1.47)
Arteriosclerotic heart disease	1.20 (0.96–1.50)
Neurological or psychiatric problem	
Cerebrovascular accident	1.50 (1.20–1.87)†
Any neuropathic pain	1.17 (0.98–1.40)
Posttraumatic stress disorder	1.09 (0.67–1.77)
Other anxiety	1.48 (1.02–2.14)†
Cognitive function	
Intact	1.00 (Reference
Mild to moderate impairment	1.24 (1.02–1.50)†
Severe impairment	0.96 (0.72–1.27)
Not assessed	1.75 (0.97–3.16)
Use of antipsychotic in residents without schizophrenia	1.52 (1.21–1.91)†
Site-level indicators	
Bed size (reference small (<60))	
Medium (60–120)	0.84 (0.60–1.18)
Large (>120)	1.02 (0.72–1.45)
Region (reference Northeast)	
Midwest	1.13 (0.77–1.65)
South	1.16 (0.80–1.69)
West	1.03 (0.69–1.53)

* Those with appropriate on-label antidepressant use (n = 48) excluded from the model.
† $P < .05$.
Wald chi-square (28) = 251.75; probability > chi-square = 0.000; log pseudolikelihood = −1761.431; pseudo coefficient of determination = 0.0612.

problematic primarily because TCAs are notorious for causing orthostatic hypotension and having both of anticholinergic effects, which can increase the risk of falls and cognitive impairment in older adults.[16–18] Under- and overdosing problems were seen in nearly 9% of residents with depression. Underdosing was most common with sertraline, trazodone, and venlafaxine. Trazodone may have been misclassified as underdosed because it may have been prescribed to manage sleep and weight loss, despite little evidence-based data to support these indications.[33] Drug–drug interactions were seen in one in four antidepressant users who were depressed. The most common drug–drug interactions were the use of multiple drugs that increase

serotonin (and thus increase the risk of serotonin syndrome); this would include the use of multiple antidepressants regardless of therapeutic intent.[34] The next most common drug–drug interactions involved the use of paroxetine, fluoxetine, or bupropion, which are potent inhibitors of CY2D6 hepatic enzymes, in combination with important substrate drugs such as metoprolol and other antidepressants (TCAs, venlafaxine), which could result in preventable adverse drug events.[35] Drug–disease interactions were just as common in this resident group and frequently involved the prescribing of antidepressants in residents with a history of a fall. The risk of falls with SSRIs is the same as that with TCAs.[36] The only potentially modifiable risk factors associated with potential inappropriate prescribing of antidepressants in this study were residents with moderate to severe pain and the prescribing of an anxiolytic or hypnotic.

To the best of the knowledge of the authors, this is one of the first studies to examine potential overuse of antidepressants in nursing home residents. In residents without depression, only a small number (48/1,190) had a FDA-approved labeled indication for the antidepressants. One explanation is that a recent study showed that U.S. physicians have limited knowledge of which indications are FDA approved versus being off-label.[37] Of potential concern is the recent report that five antidepressants are among the top 25 drugs used off label with inadequate efficacy evidence.[38] One factor associated with potential overuse was anxiety, for which there is evidence that specific antidepressants classes (and not just individual agents) may be effective; this use is supported by various nursing home organizations.[21] Finally, coprescribing of antipsychotics (in residents without schizophrenia) was associated with greater risk of antidepressant overuse.

So what are the implications of these results? One is that that there are prescribing quality problems involving antidepressants that clinicians should be aware of in VA CLCs. It is likely that similar prescribing problems are also occurring at similar levels in non-VA nursing homes given their equally high rates of antidepressant use.[5] What is not clear is the effect that this antidepressant prescribing quality has on nursing home resident outcomes. Nonetheless, it is clinically sensible to consider ways to address this quality prescribing problem. Three recently published articles describe successful approaches used in randomized controlled trials (academic detailing, pharmacist interventions, multidisciplinary teamwork, computerized decision support systems) to improve prescribing of psychotropic medications for nursing home residents,[39–41] although none of these studies examined changing the quality of antidepressant prescribing. In part to address this concern, the VA is launching a variety of initiatives, including increasing the availability and integration of psychology and psychiatric services in CLCs and increasing staff education. Similar initiatives in non-VA nursing homes will be also be necessary to address the stigma associated with diagnosing and treating psychiatric problems in nursing homes and historically low reimbursement rates for nonpsychiatrist providers.

This study has a number of potential limitations. There is potential misclassification because an independent research psychiatrist did not diagnose depression. Instead, those with depression were classified according to ICD-9 codes or severe depressive symptoms based on MDS data. Examining alternative classifications of depression, including shortening the lookback period for ICD-9 codes to 6 months and using the listing of depression in the MDS, did not substantially change the depression sample. The application of explicit criteria to evaluate the quality of prescribing is limited because they cannot take into account individual resident characteristics. In addition, the rate of potential underuse may be somewhat inflated because residents may have been receiving effective nonpharmacological treatment that this and other studies did not capture. Some explicit guideline criteria published in 2006 or later were also applied to data from 2004/05, which does not allow for prior dissemination of this information to providers. Finally, it is unclear what the generalizability of the current findings are to non-VA nursing home settings, given that the majority of their residents are older women and that the use of some antidepressant medications may be different in VA because of their use of a national formulary.

Despite these potential limitations, potential problems with the use of antidepressants were observed frequently in older U.S. veteran nursing home residents. Future studies are needed to examine the true risks and benefits of antidepressant use in nursing homes.

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Author Contributions: Dr. Hanlon conceived of and designed the study, acquired the data, supervised the analyses and interpretation of the data, and drafted the initial manuscript. Mr. Wang performed the analyses and assisted in the interpretation of data and preparation of the manuscript. Dr. Castle served as an expert on the creation and use of MDS scales as important covariates; contributed to the design, analyses, and interpretation of data for this study; and assisted in preparing the manuscript. Drs. Handler, Semla, Pugh, Berlowitz, and Dysken served on the expert panel that created the explicit criteria for evaluating potentially inappropriate antidepressant use, and all contributed to the design, analyses, and interpretation of data for this study and assisted in preparing the manuscript. Dr. Stone assisted in the development of the study design and analytical plan, oversaw the statistical analyses performed by Mr. Wang, contributed to the interpretation of data for this study, and assisted in preparing the manuscript.

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APPENDIX I

Table A1. Explicit Criteria for Antidepressant Use in Older Nursing Home Residents

Class and Agent	Selection	Minimum/Maximum Daily Dosage (mg/d)	Drug–Drug Interaction to Avoid	Drug–Disease Interactions*	Therapeutic Duplication
Miscellaneous antidepressant					
Bupropion	Recommended	150–300	CYP2D6 substrates[†]	Seizure disorder	NA
Mirtazapine	Recommended	15–45 (30 if estimated creatinine clearance <30 mL/min)	Clonidine, other drugs that ↑ serotonin[‡]	None	NA
Trazodone	Recommended	25–150	Other drugs that ↑ serotonin[‡]	None	NA
Methylphenidate	Recommended	5–20	Monoamine oxidase inhibitors	Hypertension, seizure disorder, arrhythmia, long QT interval	Other amphetamines and modafinil
Serotonin-norepinephrine reuptake inhibitor					
Venlafaxine	Recommended	50–225	Other drugs that ↑ serotonin[‡]	Hypertension	NA
SSRI					
Citalopram	Recommended	10–40	Other drugs that ↑ serotonin[‡]	Falls	Concurrent SSRI
Fluoxetine	Recommended	10–40	CYP2D6 substrates,[†] other drugs that ↑ serotonin,[‡] phenytoin	Falls	Concurrent SSRI
Paroxetine	Recommended	10–40	Anticholinergics,[‡] CYP2D6 substrates,[†] other drugs that ↑ serotonin[‡]	Falls	Concurrent SSRI
Sertraline	Recommended	50–200	Other drugs that ↑ serotonin[‡]	Falls	Concurrent SSRI
TCA					
Amitriptyline	Not recommended[1]	10–75	Anticholinergic,[§] bupropion, clonidine, other drugs that ↑ serotonin[‡]	Benign prostatic hypertrophy, constipation, dementia, falls, heart block, orthostatic hypotension	Concurrent TCA
Desipramine	Recommended	10–75	Anticholinergic,[§] bupropion, clonidine, other drugs that ↑ serotonin[‡]	Benign prostatic hypertrophy, constipation, dementia, falls, heart block, orthostatic hypotension	Concurrent TCA
Doxepin	Not recommended	10–75	Anticholinergic,[§] bupropion, clonidine, other drugs that ↑ serotonin[‡]	Benign prostatic hypertrophy, constipation, dementia, falls, heart block, orthostatic hypotension	Concurrent TCA
Nortriptyline	Recommended	10–75	Anticholinergic,[§] bupropion, clonidine, other drugs that ↑ serotonin[‡]	Benign prostatic hypertrophy, constipation, dementia, falls, heart block, orthostatic hypotension	Concurrent TCA

* Diseases were determined from admission Minimum Data Set (version 2.0) assessments and through the use of specific *International Classification of Diseases, Ninth Revision*, codes. Although this approach may not be highly sensitive, it is likely to be highly specific.

† CYP2D6 substrates (metoprolol, tricyclic antidepressants, venlafaxine).

‡ Other nonantidepressant drugs that increase serotonin that in combination with specific antidepressants increase the risk of serotonin syndrome (buspirone, dextromethorphan, meperidine, sumatriptan, tramadol).

§ Nonantidepressant drugs with anticholinergic activities included antiarrhythmic (disopyramide), anti-emetic and anti-vertigo (meclizine, prochlorperazine), antiparkinsonian (trihexyphenidyl), antipsychotic (all conventional antipsychotics, olanzapine, quetiapine), antispasmodic (e.g., belladonna, oxybutynin), cold and allergy drug (e.g., hydroxyzine and other first-generation antihistamines), sleep aid (diphenhydramine), and skeletal muscle relaxant (cyclobenzaprine and methocarbamol).

SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.