



A real-world analysis of antidepressant medications in US veterans aged 60 years and older: a comparative analysis

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Aim: To compare the safety and efficacy of antidepressants (AD) among older adults with major depressive disorder (MDD) by assessing treatment change, augmentation and hospitalization rates. **Methods:** This retrospective study analyzed data from the Veterans Affairs (VA) database, including 142,138 patients aged ≥ 60 years diagnosed with MDD. Patients prescribed bupropion, citalopram, duloxetine, escitalopram, fluoxetine, mirtazapine, paroxetine, sertraline, or venlafaxine were included. Outcomes were treatment change, augmentation and hospitalization rates. Hazard ratios (aHRs) were calculated using sertraline as the reference. **Results:** Of the patients, 39.6% required augmentation, 18.1% changed antidepressant treatment and 13.3% were hospitalized. The corresponding incidence rate was 544, 124 and 122 events per 1000 person-years. Compared with sertraline, mirtazapine users had the highest AD change risk (aHR 1.34, 95% CI: 1.29–1.40), while duloxetine users had the lowest (aHR 0.87, 95% CI: 0.83–0.92). Duloxetine also had the lowest augmentation risk (aHR 0.89, 95% CI: 0.86–0.92). Mirtazapine users also had the highest risks of augmentation (aHR 1.15, 95% CI: 1.12–1.18) and hospitalization (aHR 1.14, 95% CI: 1.07–1.23). Bupropion had the lowest hospitalization risk (aHR 0.77, 95% CI: 0.71–0.84). **Conclusion:** Antidepressant choice significantly influences treatment outcomes in older adults with MDD. Duloxetine demonstrated the best profile with the lowest risks of AD change and augmentation, while mirtazapine posed the highest risks of all three outcomes. Personalized treatment strategies are crucial to improving outcomes in this population.

Plain language summary

What is this article about? This article looks at how different antidepressants work for people aged 60 years or older who have major depressive disorder (MDD), a common and serious mental health condition. Older adults often experience unique challenges with depression, including side effects from medications and a higher likelihood of needing to change treatments. The study analyzed real-world data from the US Department of Veterans Affairs to better understand three key outcomes for older adults taking antidepressants:

1. How often they change antidepressant.
2. How often they need additional medications (augmentation).
3. How often they are hospitalized.

What were the results? The study found that:

- **Changing antidepressant:** About 18% of patients changed their antidepressant. Duloxetine was the least likely to be changed, while mirtazapine and citalopram had the highest risks of being changed.
- **Adding medications (augmentation):** Nearly 40% of patients needed an additional medication. Duloxetine and bupropion were the least likely to need augmentation, while mirtazapine had the highest risk.
- **Hospitalization:** Only 13.3% of patients were hospitalized. Mirtazapine was associated with the highest risk of hospitalization, while bupropion had the lowest.

What do the results of the study mean? The study highlights that not all antidepressants work the same for older adults. Some medications are more likely to require changes or additional treatments, and some are linked to higher risks of hospitalization. This information can help doctors make better decisions when prescribing antidepressants to older patients, balancing the potential benefits with the risks of side effects or complications. Importantly, the study does not recommend one antidepressant over another but aims to provide a clearer understanding to guide treatment choices. This summary is intended to make the study more accessible to patients, caregivers and advocates who want to understand how depression treatments work in older adults.

Sharable abstract: Antidepressants impact older adults differently. Our study reveals key differences in antidepressant change, augmentation and hospitalization risks. Insights for tailored depression care! #MentalHealth #DepressionCare #Geriatrics

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The burden of depression continues to rise despite a multitude of studies aimed at reducing the impact of depression [1–3]. An estimated 21 million adults in the USA have had at least one major depressive episode [4], with an estimated economic burden of more than \$330 billion in 2019 (equivalent to over \$400 billion in 2024 USD) [5]. There are several US FDA-approved medications that can be utilized to treat depression [6], with phase III, phase IV and meta-analyses studies demonstrating the efficacy and effectiveness compared with placebo [7–9]. Specifically, antidepressants have been demonstrated to be superior at treating depression compared with placebo, including among patients spanning a wide age gap [10]. However, the burden of depression is higher among patients 60 years of age or older compared with less than 60 years of age and presents a complex and significant challenge to healthcare [11,12]. Fortunately, antidepressants are effective in treating depression among patients 60 years of age and older [13]; however, antidepressants are associated with a higher frequency of side effects among these patients [4]. These side effects, along with the notion that the treatment may be statistically beneficial rather than clinically beneficial [14], may result in a patient changing antidepressants, augmenting their treatment or even being hospitalized. Clinical trials evaluating the treatment of depression often include observation periods of 6–12 weeks long, and patients with significant comorbidities and of older ages have been excluded from select studies [15,16]. Therefore, we aimed to utilize real-world data among a national cohort of patients with major depression disorder (MDD) to evaluate patients 60 years of age and older to evaluate the frequency of antidepressant treatment change, treatment augmentation and hospitalization.

Materials & methods

Data source

This national retrospective cohort study was conducted using data from the US Department of Veterans Affairs (VA). The Veterans Affairs Informatics and Computing Infrastructure (VINCI) was utilized to obtain individual-level information of structured claims data on demographics, administrative claims and pharmacy dispensation. The completeness, utility, accuracy, validity and access methods are described on the VA website, <http://www.virec.research.va.gov> (search term VINCI). The study was conducted in compliance with the Department of Veterans Affairs requirements and received Dorn Research Institute Institutional Review Board, Research and Development and VINCI approval. The study utilized inpatient and outpatient data consisting of claims coded with International Classification of Diseases (ICD) revision 9-CM, revision 10-CM and pharmacy data.

Study design

This study employed a retrospective cohort study design utilizing administrative claims data from 1 October 1999 to 31 December 2023. The target population was patients with a diagnosis of MDD (ICD-9: 296.2X, 296.3X, ICD-10: F32.XX, F33.XX) at any point prior to 10 December 2023, and who were prescribed their first antidepressant on or after the diagnosis between 1 January 2000 and 30 September 2023 (see [Supplementary Table 1](#) for complete list of antidepressants). Additionally, all patients had to be 60 years old or older at index and at least 6 months of enrollment prior to index. Patients diagnosed with bipolar disorder or schizophrenia prior

to index were excluded (ICD9: 295, 296.0, 296.4, 296.5, 296.6, 296.7, 296.8; ICD10: F20.x, F31.x). Patients were also excluded from the study if they were prescribed multiple antidepressants at index, had missing data for demographics including sex, or had an observation period of less than 90 days from index to death or 30 September 2023.

All patients were followed from day 1 after index until the earliest loss to follow-up, death, the discontinuation of the index drug, or 30 September 2023, whichever comes first [17,18]. Discontinuation date is defined as the last day the initial antidepressant was supplied and not re-dispensed within 90 days. If discontinuation occurred prior to death or 30 September 2023, then an additional 90 days of pharmaceutical dispenses were utilized to determine if a different antidepressant was prescribed (constituting a change). Antidepressants with 5000 or more prescriptions were included in the study [19]. Additionally, each patient's initial dose was required to be more than 50% of the recommended starting dose of the specific antidepressant [20,21].

Outcomes

This study had three primary outcomes: antidepressant treatment change, treatment augmentation and hospitalization. Changing antidepressants was defined as the dispensing of an antidepressant different from the initially prescribed antidepressant any time between discontinuation of the initial antidepressant and 90 days later. Augmenting was defined as being dispensed any additional antidepressant, mood stabilizer, antipsychotic, antianxiety or stimulant after index and before discontinuation (see [Supplementary Table 2](#) for list of included augmentations). Hospitalization was defined as having had an inpatient encounter after index up to the discontinuation date. These outcomes were analyzed independently.

Covariate data

The main covariates used in this study were age, sex and race. These variables along with patient index year, mental health conditions (e.g., suicidal ideation, anxiety, drug/alcohol abuse) were used to ensure that comparisons between treatment groups adjusted for potential health differences. The Charlson Comorbidity Index (CCI) and BMI category were also calculated.

Statistical analysis

Baseline covariates were compared between treatment groups. Categorical variables (e.g., BMI category, sex, race) were compared using the chi-square test. Continuous variables (e.g., age, CCI) were compared using one-way ANOVA. Standardized differences were also calculated to compare each baseline variable. For each outcome (including psychological hospitalization), percent impacted, incident rates were calculated and then univariate and multivariate proportional hazard models were calculated to produce a hazard ratio HR (and adjusted hazard ratio aHR), individually comparing the most common antidepressant, sertraline, to each of the other antidepressants. Subanalysis was performed by restricting the amount of time each patient was in the study to a minimum of 90-days and maximum of 730-days. Data were analyzed using SAS version 9.4 and R version 4.1.2.

Results

There were 3,317,247 patients diagnosed with major depression disorder identified prior to 10 December 2023, and 1,015,940 patients were prescribed an antidepressant on or after their first depression diagnosis. A total of 267,854 patients were 60 years of age or older at index and after applying inclusion/exclusion criteria, there were 142,138 patients included in the analysis, who were initially prescribed one of bupropion, citalopram, duloxetine, escitalopram, fluoxetine, mirtazapine, paroxetine, sertraline or venlafaxine. [Table 1](#) provides an overview of attrition conditions used to create the cohort size.

[Table 2](#) provides the baseline demographic and health-related characteristics of the cohort. The average age of the population was 70.42 years, and the mean Charlson Comorbidity Index score was 1.30. The cohorts were 95.73% male, 73.19% white and 15.82% black. The BMI distribution showed that the largest proportion had BMI of 30+ (39.632%), followed by 25–29.9 (36.061%), 18.5–24.9 (21.668%) and <18.5 (1.581%). [Table 3](#) provides the overall percentage of patients who experienced each outcome, as well as the incidence rate per 1000 person-years, while [Table 4](#) provides *p*-values and standardized differences of the overall differentiation between treatment groups for each baseline characteristics. [Supplementary Table 3](#) provides a complete breakdown of baseline comorbidities. [Supplementary Table 4](#) has the rate and incidence rate of each outcome, including psychological hospitalization (ICD codes in [Supplementary Table 5](#)).

Table 1. Attrition.

Condition	Count
Ever diagnosed with major depression disorder prior to December 10, 2023 (ICD-9: 296.2X, 296.3X, ICD-10: F32.XX, F33.XX)	3,317,247
Prescribed any antidepressant on or after first depression diagnosis date (Supplementary Table 1)	1,015,940
Sex variable available	1,015,879
Age (years) ≥ 60	267,854
Not diagnosed with bipolar disorder or schizophrenia prior to index (ICD9: 295, 296.0, 296.4, 296.5, 296.6, 296.7, 296.8 ICD10: F20, F31)	256,957
6 months of enrollment prior to index (first antidepressant dispense)	215,750
Observation period at least 90 days (from index to death or 30 September 2023)	206,350
Only prescribed 1 antidepressant at index	185,591
Initial Index AD is 1 of the 10 with frequency greater than 5000	179,230
Initial AD prescription more than 50% of the recommended starting depression treatment dosage [†]	146,008
Not prescribed trazodone (since count dropped below 5000)	142,613
Initial antidepressant dispense date on or after 1 January 2000 [†]	142,138

[†]The latest index date is 2 July 2023, guaranteeing at least 90 days of inclusion.
AD: Antidepressant.

Table 2. Overall cohort baseline characteristics.

Variable	Value
Mean age (SD)	70.422 (8.152)
Charlson comorbidity index (SD)	1.301 (1.831)
Index year (median)	2017
Race	
Black	21,584 (15.8%)
Other/unknown	16,527 (11.6%)
White	104,027 (73.2%)
Sex, female	6077 (4.3%)
Sex, male	136,061 (95.7%)
BMI	
<18.5	2248 (1.6%)
18.5–24.9	30,798 (21.7%)
25–29.9	51,256 (36.1%)
30+	56,332 (39.6%)
Missing	1504 (1.1%)
ADHD	666 (0.5%)
Drug abuse	4746 (3.3%)
Alcohol abuse	11,570 (8.1%)
Suicide ideations	3571 (2.5%)
Anxiety	27,448 (19.3%)
Sleep disorder	25,553 (18.0%)
Discontinued	120,020 (84.4%)

ADHD: Attention-deficit/hyperactivity disorder; SD: Standard deviation.

Table 3. Outcomes.

	Count (%)	Incidence rate per 1000 person years (95% CI)
Hospitalized	18,969 (13.3%)	122 (120, 124)
Augmented AD	562,86 (39.6%)	544 (540, 549)
Changed AD	25,666 (18.1%)	124 (123, 126)

AD: Antidepressant; CI: Confidence interval.

Table 4. Baseline comorbidities/conditions.

Variable	Bupropion (n = 11,835)	Citalopram (n = 21,446)	Duloxetine (n = 14,161)	Escitalopram (n = 11,695)	Fluoxetine (n = 7604)	Mirtazapine (n = 17,368)	Paroxetine (n = 5621)	Sertraline (n = 44,848)	Venlafaxine (n = 7560)	p-value	Standardized difference
Age mean (SD)	67.7 (6.50)	70.14 (8.36)	69.76 (7.52)	71.37 (8.31)	68.77 (7.25)	72.67 (9.22)	70.09 (7.68)	70.88 (8.14)	69.3 (7.53)	<0.001	0.622
Charlson comorbidity index	1.07 (1.56)	1.22 (1.68)	1.51 (1.98)	1.23 (1.76)	1.05 (1.53)	1.65 (2.26)	1.06 (1.57)	1.31 (1.81)	1.19 (1.72)	<0.001	0.309
Index year (median)	2018	2009	2019	2019	2017	2017	2014	2017	2016	<0.001	1.888
Race											
Black	1743 (14.7%)	2492 (11.6%)	2422 (17.1%)	1693 (14.5%)	873 (11.5%)	3799 (21.9%)	594 (10.6%)	7222 (16.1%)	746 (9.9%)	<0.001	0.332
Other/unk.	1163 (9.8%)	2887 (13.5%)	1524 (10.8%)	1165 (10.0%)	978 (12.9%)	2082 (12.0%)	842 (15.0%)	4993 (11.1%)	893 (11.8%)		
White	8929 (75.4%)	16,067 (74.9%)	10,215 (72.1%)	8837 (75.6%)	5753 (75.7%)	11487 (66.1%)	4185 (74.5%)	32,633 (72.8%)	5921 (78.3%)		
Sex, female	659 (5.568%)	672 (3.133%)	962 (6.793%)	659 (5.635%)	419 (5.51%)	451 (2.597%)	225 (4.003%)	1569 (3.498%)	461 (6.098%)	<0.001	0.199
Sex, male	11,176 (94.432%)	20,774 (96.867%)	13,199 (93.207%)	11,036 (94.365%)	7185 (94.49%)	16917 (97.403%)	5396 (95.997%)	43,279 (96.502%)	7099 (93.902%)		
BMI											
<18.5	141 (1.2%)	302 (1.4%)	128 (0.9%)	122 (1.0%)	68 (0.9%)	798 (4.6%)	80 (1.4%)	538 (1.2%)	71 (0.9%)		
18.5–24.9	2311 (19.5%)	4640 (21.6%)	2237 (15.8%)	2322 (19.9%)	1339 (17.6%)	6313 (36.3%)	1193 (21.2%)	9093 (20.3%)	1350 (17.9%)		
25–29.9	4088 (34.5%)	7967 (37.1%)	4663 (32.9%)	4273 (36.5%)	2688 (35.4%)	6099 (35.1%)	2132 (37.9%)	16,651 (37.1%)	2695 (35.6%)	<0.001	0.576
30+	5185 (43.8%)	8347 (38.9%)	7001 (49.4%)	4822 (41.2%)	3416 (44.9%)	3968 (22.8%)	2154 (38.3%)	18,093 (40.3%)	3346 (44.3%)		
Missing	110 (0.9%)	190 (0.9%)	132 (0.9%)	156 (1.3%)	93 (1.2%)	190 (1.1%)	62 (1.1%)	473 (1.1%)	98 (1.3%)		
ADHD	223 (1.9%)	50 (0.2%)	70 (0.5%)	54 (0.5%)	40 (0.5%)	51 (0.3%)	7 (0.1%)	123 (0.3%)	48 (0.6%)	<0.001	0.181
Drug abuse	485 (4.1%)	500 (2.3%)	527 (3.7%)	316 (2.7%)	244 (3.2%)	971 (5.6%)	129 (2.3%)	1334 (3.0%)	240 (3.2%)	<0.001	0.170
Alcohol abuse	1056 (8.9%)	1555 (7.3%)	902 (6.4%)	839 (7.2%)	633 (8.3%)	1999 (11.5%)	402 (7.2%)	3615 (8.1%)	569 (7.5%)	<0.001	0.179
Suicide ideations	179 (1.5%)	280 (1.3%)	384 (2.7%)	362 (3.1%)	180 (2.4%)	717 (4.1%)	77 (1.4%)	1227 (2.7%)	165 (2.2%)	<0.001	0.173
Anxiety	1909 (16.1%)	3617 (16.9%)	2396 (16.9%)	2489 (21.3%)	1343 (17.7%)	3588 (20.7%)	1269 (22.6%)	9231 (20.6%)	1606 (21.2%)	<0.001	0.165
Sleep disorder	2185 (18.5%)	2451 (11.4%)	3539 (25.0%)	2388 (20.4%)	1246 (16.4%)	3385 (19.5%)	702 (12.5%)	8325 (18.6%)	1332 (17.6%)	<0.001	0.358
Discontinued	10,303 (87.1%)	19,470 (90.8%)	11,118 (78.5%)	9045 (77.3%)	6421 (84.4%)	15206 (87.5%)	4925 (87.6%)	37,222 (83.0%)	6310 (83.5%)	<0.001	

† Medians compared using a Kruskal–Wallis test.
ADHD: Attention-deficit/hyperactivity disorder; SD: Standard deviation; unk.: Unknown.

Table 5. Outcomes by treatment.

Variable	Bupropion (n = 11,835)	Citalopram (n = 21,446)	Duloxetine (n = 14,161)	Escitalopram (n = 11,695)	Fluoxetine (n = 7604)	Mirtazapine (n = 17,368)	Paroxetine (n = 5621)	Sertraline (n = 44,848)	Venlafaxine (n = 7560)
Hospitalized count (%)	1009 (8.5%)	3244 (15.1%)	1723 (12.2%)	1249 (10.7%)	961 (12.6%)	2979 (17.2%)	697 (12.4%)	6156 (13.7%)	951 (12.6%)
Hosp. IR (95% CI)	80 (80, 90)	130 (130, 140)	120 (120, 130)	100 (90, 100)	100 (100, 110)	220 (210, 230)	90 (90, 100)	120 (120, 120)	90 (90, 100)
Aug. Count (%)	4076 (34.4%)	9765 (45.5%)	4340 (30.6%)	4382 (37.5%)	3144 (41.3%)	6695 (38.5%)	2671 (47.5%)	17,749 (39.6%)	3464 (45.8%)
Aug. IR (95% CI)	540 (520, 560)	630 (610, 640)	410 (390, 420)	490 (470, 500)	500 (480, 520)	760 (740, 780)	600 (570, 620)	510 (500, 520)	560 (540, 580)
Changed count (%)	1964 (16.6%)	4943 (23.0%)	1844 (13.0%)	1834 (15.7%)	1365 (18.0%)	3189 (18.4%)	1283 (22.8%)	7713 (17.2%)	1531 (20.3%)
Changed IR (95% CI)	120 (120, 130)	150 (140, 150)	100 (100, 100)	120 (110, 120)	110 (100, 120)	160 (160, 170)	140 (130, 140)	120 (110, 120)	110 (110, 110)

† IR CI Calculated using the Poisson distribution (per 1000 person-years).
Aug.: Augmented; CI: Confidence interval; Hosp.: Hospitalized; IR: Incidence rate.

Table 6. Unadjusted hazard ratios (ref = sertraline).

Drug	Change HR (95% CI)	Augmentation HR (95% CI)	All hospitalization HR (95% CI)
Bupropion	1.05 (1.00, 1.11) [†]	0.95 (0.92, 0.98) [†]	0.67 (0.63, 0.72)
Citalopram	1.33 (1.28, 1.38) [†]	1.23 (1.20, 1.26) [†]	1.11 (1.06, 1.16) [†]
Duloxetine	0.81 (0.77, 0.85) [†]	0.76 (0.73, 0.78) [†]	0.95 (0.90, 1.00)
Escitalopram	0.94 (0.90, 0.99) [†]	0.92 (0.89, 0.95) [†]	0.78 (0.74, 0.83) [†]
Fluoxetine	0.99 (0.93, 1.04)	1.03 (0.99, 1.06)	0.86 (0.81, 0.93) [†]
Mirtazapine	1.29 (1.24, 1.35) [†]	1.20 (1.17, 1.23) [†]	1.60 (1.53, 1.67) [†]
Paroxetine	1.24 (1.17, 1.32) [†]	1.24 (1.19, 1.29) [†]	0.82 (0.76, 0.89) [†]
Venlafaxine	1.07 (1.02, 1.14) [†]	1.20 (1.16, 1.24) [†]	0.83 (0.77, 0.89) [†]

† Indicates statistical significance.
CI: Confidence interval; HR: Hazard ratio.

Table 7. Adjusted hazard ratios (Ref = sertraline).

Drug	Change aHR (95% CI)	Augmentation aHR (95% CI)	All hospitalization aHR (95% CI)
Bupropion	0.99 (0.94, 1.04)	0.96 (0.93, 0.99) [†]	0.77 (0.71, 0.84) [†]
Citalopram	1.21 (1.16, 1.25) [†]	1.00 (0.97, 1.03)	1.04 (0.97, 1.11)
Duloxetine	0.87 (0.83, 0.92) [†]	0.89 (0.86, 0.92) [†]	1.06 (0.98, 1.14)
Escitalopram	1.03 (0.98, 1.09)	1.04 (1.01, 1.08) [†]	0.96 (0.88, 1.05)
Fluoxetine	0.93 (0.88, 0.98) [†]	0.99 (0.95, 1.03)	0.908 (0.9, 1.07)
Mirtazapine	1.34 (1.29, 1.40) [†]	1.15 (1.12, 1.18) [†]	1.14 (1.07, 1.23) [†]
Paroxetine	1.17 (1.10, 1.24) [†]	1.08 (1.03, 1.12) [†]	0.82 (0.74, 0.92) [†]
Venlafaxine	1.00 (0.95, 1.06)	1.12 (1.08, 1.16) [†]	0.92 (0.84, 1.00)

† Indicates statistical significance.
aHR: Adjusted hazard ratio; CI: Confidence interval.

Treatment change

Table 3 shows that a treatment change occurred in 18.1% of patients during the study period, with an incidence rate of 124 per 1000 person-years. Tables 4 & 5 present a comparative analysis of the baseline covariates across different initial antidepressant medications. Changing antidepressants after discontinuation was most likely to occur for patients prescribed citalopram (23.049%) and least likely to occur for patients prescribed duloxetine (13.022%). Duloxetine patients also had the lowest incidence rate (100 per 1000 person-years), but mirtazapine had the highest incidence rate (160 per 1000 person-years). Table 6 gives the unadjusted hazard ratios for each outcome, but once adjusting for baseline covariates and taking time into account (average follow-up time can be found in Supplementary Table 6), Table 7 shows that mirtazapine had a significantly higher risk of a treatment change

with an aHR of 1.34 (95% CI: 1.29, 1.40) compared with sertraline. This was the highest risk of any treatment. Additionally, patients prescribed citalopram saw a 21% higher adjusted risk of changing antidepressants compared with patients prescribed sertraline (95% CI: 1.16, 1.25). Patients prescribed duloxetine had a significantly lower risk of an AD treatment change (aHR 0.87; 95% CI: 0.83, 0.92) and represented the lowest adjusted hazard ratios of all the treatment options. The fluoxetine cohort also had a low risk of AD change (aHR 0.93; 95% CI: 0.88, 0.98), while patients who were prescribed paroxetine had a 17% higher risk of change (95% CI: 10% to 24%) than sertraline patients.

Augmentation

Treatment augmentation occurred in 39.6% of patients during the study period and had an incidence rate of 544 per 1000 person-years (Table 3). Table 5 shows that the duloxetine cohort experienced the least treatment augmentation, with 30.6% of patients in this cohort receiving augmentation and also had the lowest incidence rate at 0.41 per patient-year. Paroxetine patients experienced the most augmentation (47.5%), but mirtazapine has the highest incidence rate at 760 per 1000 person-years. Once adjusting for baseline covariates and taking follow-up time into account, Table 7 shows that mirtazapine had a significantly higher risk of augmentation with an aHR of 1.15 (95% CI: 1.12, 1.18) compared with sertraline. Bupropion had significantly lower risk of augmentation (aHR = 0.96; 95% CI: (0.93, 0.99)). Patients prescribed duloxetine also had a significantly lower risk of augmentation compared with sertraline with an aHR of 0.89 (95% CI: 0.86, 0.92) and was the lowest adjusted hazard ratios of all the treatment options. Patients prescribed escitalopram had a slightly higher risk of augmentation compared with patients taking sertraline with an aHR of 1.04 (95% CI: 1.01, 1.08), and patients who were prescribed paroxetine had an 8% higher risk of augmentation (95% CI: 3% to 12%) than sertraline patients. Lastly, venlafaxine patients had a 12% higher risk of augmentation compared with the sertraline patients (95% CI: 8% to 16%).

Hospitalization

Hospitalization occurred in 13.35% of patients during the study period with an incidence rate of 122 per 1000 person-years. Table 5 shows that 17.2% of patients in the mirtazapine cohort were hospitalized, and only 8.5% of patient in the bupropion cohort were hospitalized. This finding remains consistent when looking at incidence rates, where hospitalization incidence rate was 220 per 1000 person-years for mirtazapine patients and just 80 per 1000 person-years for bupropion patients. Once adjusting for baseline covariates and continuing to take time into account, mirtazapine had a significantly higher risk of hospitalization with an aHR of 1.14 (95% CI: 1.07, 1.23) compared with sertraline. This was the highest risk of hospitalization for any of the treatment groups. Bupropion had significantly lower risk hospitalization (aHR = 0.77; 95% CI: [0.71, 0.84]) compared with sertraline. This was the smallest risk of hospitalization of any of the treatments. Patients who were prescribed paroxetine had a 18% lower risk of hospitalization compared with sertraline patients (95% CI: 8% to 26%). No other comparison to sertraline was significant. Secondary analysis specifically analyzing psychological hospitalization was performed and Supplementary Table 7 highlights the hazard ratios for each treatment.

Supplementary Table 8 presents the adjusted hazard ratios for changing treatment, augmenting treatment, or being hospitalized within 730 days (2 years) of treatment, provided the patient did not experience the outcome within the first 90 days of the index date. Although some results differed from Table 7, the key findings remained consistent.

Discussion

Depression imposes a significant healthcare burden and is a leading cause of medical disability. The high incidence and prevalence of depression leads to a decreased quality of life, increased risk of chronic diseases and higher mortality rates [22–26]. Additionally, the economic impact is substantial, with increased healthcare costs, lost productivity and associated comorbidities. The FDA has approved medications for treating depression that have been shown to be more effective than placebo; however, select clinical trials have included short observation periods (e.g., 6–12 weeks) and excluded patients with significant comorbidities. This study evaluated the utilization of antidepressants among patients 60-years of age and older to measure antidepressant treatment change, treatment augmentation and overall hospitalization. The results of our study demonstrated a high overall rate of treatment outcomes consisting of 18.1% experiencing a treatment change, 39% experiencing a treatment augmentation and 13.3% experiencing a hospitalization (also reported by antidepressant and as incidence rates). Although clinical trials demonstrate superior

outcomes, this real-world study demonstrates a high rate of medication alteration (change/augmentation) that can impact treatment success.

While some, similar, studies allowed for patients to be treated with multiple antidepressants at index [27], this study is modeled after those that only allow for one antidepressant to be dispensed at index to focus on individual antidepressants [19]. The nine antidepressants highlighted in this study are some of the most commonly prescribed antidepressants and the same that were included in other studies, such as Pradier, McCoy, *et al.*, who predicted treatment dropout [28]. Additionally, a multitude of studies highlight obesity as a risk factor for depression [29–32], and the BMI group 30+ had the largest percentage of patients. A recent study by Ishtiak-Ahmed *et al.* also examined real-world outcome of antidepressant use among older adults, focusing on a nationwide cohort in Denmark [33]. They found that mirtazapine and venlafaxine had higher risks of adverse outcomes compared with sertraline users. This similarity to our study comes despite different patient populations, healthcare systems and temporal contexts.

While no study was exactly like ours, Hsu, *et al.* had also had similarities in that they measured the aHR of changing, augmenting and hospitalizations [19]. After adjusting for the baseline covariates, our study showed that mirtazapine had the highest risk of hospitalization. The adjusted risk was 14% higher (95% CI: 7% to 23%) than patients who took sertraline. Bupropion continued to have the lowest risk of hospitalization. These results are more consistent with Hsu, *et al.*, who found that the adjusted risk of hospitalization was 33% (95% CI: 13% to 57%) higher for mirtazapine patients than sertraline patients. They also found that bupropion patients had a lower risk of hospitalization than sertraline patients, though the result was not statistically significant.

However, not all of the results in this study are consistent with theirs. For example, they found that duloxetine had a significantly higher risk of changing antidepressants compared with sertraline and that mirtazapine did not have a significant difference in risk of changing compared with sertraline. Our study showed that duloxetine had the lowest risk of changing antidepressants, and that mirtazapine had a significantly high risk of changing. Our study also had differing results when comparing antidepressant augmentation. Some potential reasons for these differences are that their patient population is from Taiwan with a date range from 1997 to 2013. Their study also consisted of more females than males, whereas this study consisted mostly of white males with data up until the end of 2023 when depression treatment patterns have constantly evolved. One other key difference between this study and prior work is that Hsu, *et al.* focused only on psychiatric hospitalizations rather than all hospitalizations. Since many of the side effects of antidepressants are not purely psychological, this study chose to use all hospitalization as a main outcome of interest in order to capture it all and not limit the outcome to the indistinct definition of psychiatric hospitalization. In this study, subanalysis was performed where psychiatric hospitalization was defined by any inpatient diagnosis of schizophrenia, dementia, bipolar disorder, drug abuse, alcohol abuse, suicide ideation, anxiety, or sleep disorders (see [Supplementary Table 5](#) for complete list of codes). The results are provided in [Supplementary Table 7](#) which shows that nearly every treatment's aHR for psychological hospitalization was statistically comparable to the aHR for all hospitalization.

As is the case with all health insurance claims database analysis, there are limitations, particularly proper documenting, and coding. However, the major benefit to database analysis is the availability of a large sample. This study began with over 3 million patients with MDD, and despite having restrictive inclusion criteria over 140,000 patients were eligible for analysis. Since the study was limited to only the available data, it was also possible that the first time a patient was prescribed an antidepressant in the available data was not the actual first antidepressant they were prescribed in their life. To minimize the risk of this occurring, each patient had to have a minimum enrollment time of 6-months prior to their first antidepressant prescription and had to have an official MDD diagnosis prior to that to show that they were utilizing VA care. Even if a patient was prescribed an antidepressant prior to enrolling in VA healthcare, the wash out period would have been long enough where the treatment would have been absent from patient's system prior to this study's defined index [34,35]. Unfortunately, there is no way to be certain that the veteran did not seek care outside of the VA. Fortunately, antidepressants require a prescription, so the patient could not have purchased the treatment over the counter. One of the main benefits of a retrospective study with over 140,000 unique patients is that even if a patient was misclassified or misdiagnosed and the inclusion methodology could not account for it, the signals from the study are extremely unlikely to change, further validating the study's results.

Another limitation is that in general, more women are treated with antidepressants than men [36], but in this study, 95% of all patients in the are men. This difference is likely because the population of veterans in the database consists mostly of older white males. This also plays a role as to why each treatment had a substantially larger percent of white patients compared with black patients; moreover, white people with depression were more likely

than all other races to receive treatment [37]. Though it is not possible to change the data's population, the main models of this study adjusted for race and gender; however, it must be noted that the results from this study may not be representative of all geriatric patients with MDD, receiving treatment.

In the primary analysis, every patient had to have at least 90 days in the study, but the outcomes could occur within 90 days of index. Though not applicable for many patients, we performed a subanalysis where patients experiencing the outcome prior to 90 days were removed, and the maximum observation time was set at 730 days, so any patient who had not yet reached the outcome of interest by 730 days after index was right censored. [Supplementary Table 8](#) provides the aHR from this subanalysis, and the majority of the aHR were unchanged in this analysis compared with the adjacent aHR with no time restraints. Mirtazapine still had a significantly higher risk of change, augmentation and hospitalization compared with sertraline and a higher risk of each outcome compared with the other treatments. Some of the aHR changed significance after altering the time constraints (compared with [Table 7](#)), but the majority of the comparisons remained unchanged. The only comparison that changed signs was bupropion's augmentation. In the original analysis, bupropion had a significantly lower risk of augmentation than sertraline; however, when including the time restraints, bupropion had a significantly higher risk of augmentation compared with sertraline.

This paper's purpose is to present these findings as informative and is not meant to imply that any particular antidepressant is more/less likely to cause any one of these outcomes. Rather, the goal is to show how they relate to each outcome to provide doctors, clinicians and researchers with this knowledge in hopes of aiding in the advancement of depression treatment. It is important to note that, while this research is valuable, its findings are not widely generalizable due to the predominantly older white male patient population.

Conclusion

Depression imposes a significant healthcare burden, and the high incidence and prevalence of depression leads to a decreased quality of life, increased risk of chronic diseases and higher mortality rates. We utilized real-world data among a national cohort of patients with major depression disorder (MDD) to evaluate patients 60 years of age on depression antidepressant treatment change, treatment augmentation and hospitalization. Our results demonstrate high overall rates of the treatment outcomes especially related to treatment change and augmentation. Moreover, our results found that there were significant differences in risk of outcomes between different antidepressants. The intentions of this study were not to determine which antidepressants should or should not be prescribe, nor are the conclusions meant to state which antidepressants are more effective.

Summary points

- Depression in older adults (≥ 60 years) poses unique challenges, including increased risks of side effects and treatment alterations.
- This study used real-world data from the US Department of Veterans Affairs, analyzing over 140,000 patients with major depressive disorder.
- Three outcomes were assessed: treatment changing, treatment augmentation and hospitalization rates.
- Changing: Duloxetine had the lowest risk of being changed, while mirtazapine and citalopram had the highest.
- Augmentation: Nearly 40% of patients required additional medication; duloxetine and bupropion had the lowest risks, while mirtazapine had the highest.
- Hospitalization: 13.3% of patients were hospitalized; mirtazapine had the highest hospitalization risk, and bupropion had the lowest.
- The findings highlight significant differences in antidepressant outcomes, underscoring the importance of tailoring treatments to individual patient profiles.
- This study provides critical real-world insights beyond clinical trial settings, reflecting the complexity of treating older adults with depression.
- Limitations include a predominantly male, veteran population, which may affect the generalizability of the findings.
- Results are intended to inform clinicians, researchers and patients about antidepressant outcomes, fostering informed decision-making in depression care.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <https://bpl-prod.literatumonline.com/doi/10.57264/cer-2024-0187>

Author contributions

Each author aided in designing the framework of the analysis utilizing past experience, current research and available literature. In addition, RD Pittman performed the analysis and was the lead author. J Magagnoli and TH Cummings aided in the coding portion of analysis and paper edits. SS Sutton performed paper edits, including locating many of the manuscript's references.

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Competing interests disclosure

SS Sutton has received research grants from Boehringer Ingelheim, Gilead, EMD Serono and Alexion Pharmaceuticals, all for projects unrelated to study. SS Sutton, J Magagnoli and TH Cummings disclose support from NIH grant R01DA054992 and the South Carolina Center for Rural and Primary Healthcare for projects unrelated to this study. The authors have no other competing interests or relevant affiliations with any organization/entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors confirm all relevant ethical guidelines have been followed, and any necessary IRB and/or ethics committee approvals have been obtained.

Data sharing statement

Data were sourced from the VA database (VINCI) and are available upon reasonable request and institutional approval.

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