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ORIGINAL REPORT

Predictors of alternative antidepressant agent initiation among U. S. veterans diagnosed with depression†

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SUMMARY

OBJECTIVES Naturalistic studies comparing differences in risks across antidepressant agents must take into account factors which influence selection of specific agents and may be associated with outcomes. We examined predictors of antidepressant choice among VA patients treated for depression.

METHODS Retrospective cohort study of VA patients with depression diagnoses and a new start of one of the seven most commonly prescribed antidepressant agents between 1 April 1999 and 30 September 2004 ($n = 502\,179$). We examined the relationship between patient and facility characteristics and new starts of bupropion, citalopram, fluoxetine, mirtazapine, paroxetine, sertraline, and venlafaxine. We also examined factors associated with new starts only among patients starting selective serotonin reuptake inhibitors (SSRIs).

RESULTS Thirty-three percent of patients starting mirtazapine had at least three outpatient mental health visits in the prior year, compared to $\leq$24% of patients prescribed other antidepressants. Patients starting mirtazapine were also most likely to have received at least two other psychotropic medications in the prior year. Of the four SSRIs, 40% of the patients receiving sertraline and only 31% of those receiving fluoxetine were 65 years or older. A comorbid anxiety disorder (other than post-traumatic stress disorder) was diagnosed in 21% of paroxetine patients compared with $\leq$15% of other SSRI patients.

CONCLUSION Choice of antidepressant medication for depressed VA patients was associated with important differences in demographic and clinical variables, including psychiatric illness severity, older age, and likelihood of a comorbid anxiety disorder. These findings emphasize the importance of controlling for selection bias when using observational data to compare risks from or effect of mental health treatments.

KEY WORDS — antidepressant selection; predictors; depression diagnosis

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INTRODUCTION

Researchers, drug safety experts, and policy makers are increasingly using large clinical observational datasets to explore potential relationships between medication use and adverse outcomes. In particular, examining the relationship between specific medications and tragic, but rare, outcomes, such as suicide deaths, can often only be accomplished with large observational datasets.

However, a major limitation in using existing clinical datasets to assess potential causal links between treatments and outcomes is treatment selection in clinical settings. In these settings, treatments are selected based on physician and patient preferences rather than being randomly allocated. Thus, patients who have higher risks for poor outcomes may preferentially receive specific treatments, potentially resulting in spurious associations between these treatments and poor outcomes. Because of these challenges, several large observational studies have inaccurately identified associations between treatments and outcomes

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(e.g., hormone replacement therapy and reduced cardiac disease).[1]

Recently, concerns have emerged that antidepressant medications which are effective treatments for depression, might paradoxically *increase* suicide risks, particularly in the weeks following treatment initiation or dosage change. Pharmaceutical company data from multiple randomized controlled trials of antidepressant treatment of children, adolescents, and young adults have indicated increased rates of suicidal thinking and behaviors among individuals randomized to antidepressant treatment. However, the impact on suicide deaths is less certain.[2,3]

Because deaths from suicide are rare, large sample sizes are needed to assess potential associations between antidepressants and suicide death, and administrative data have been used for this purpose. However, to date, these studies have reported mixed results, potentially because of channeling or treatment selection biases. To draw valid conclusions based on observational studies, it is important to understand the predictors of different choices of antidepressant agent.

Prior studies have indicated that choice of antidepressant may be influenced by physician characteristics such as specialty or age and by patient characteristics such as number of previous depressive episodes or education level.[4–7] However, there may be fewer selection biases when only selective serotonin reuptake inhibitors (SSRIs) are considered as these medications are thought to have similar mechanisms of action and to have comparable efficacy in treating depression.[8,9]

In this study, we examined whether patient characteristics readily available in the VA administrative data were associated with initial choice of an antidepressant agent in VA patients diagnosed with depression. The Department of Veterans Affairs Health System (VA) is the nation's largest organized healthcare system and has information systems offering data for large-scale assessments of treatment practices and patient outcomes. Although data on prescriber characteristics are not available, data on patient mental and physical health conditions and psychotropic medication fills are readily available in VA administrative databases.

We used a unique longitudinal dataset with comprehensive diagnosis and pharmacy data for all VA patients in depression treatment between 1 April 1999 and 30 September 2004 to examine patient and facility characteristics associated with initial choice of an antidepressant agent. We hypothesized that patients receiving different antidepressant agents would differ significantly in demographic and clinical characteristics (e.g., age and illness severity) that might also be associated with treatment outcomes. If verified, this conclusion has implications for studies using administrative data to examine relationships between antidepressant treatments and outcomes and implication for quality improvement efforts aimed at standardizing antidepressant treatment practices.

METHODS

Study population and design

A retrospective cohort study was conducted to evaluate antidepressant agent choice for new antidepressant starts among patients diagnosed with depression. Data were obtained from the VA's National Registry for Depression (NARDEP) which was developed by the VA's Serious Mental Illness Treatment Resource and Evaluation Center (SMITREC) in Ann Arbor, Michigan. This study was approved by the Institutional Review Board of the Veterans Affairs Ann Arbor Health System. All patients who used the VA between 1 April 1999 and 30 September 2004, and received one or more depression diagnoses and a new start of one of the seven most commonly prescribed antidepressants (bupropion, citalopram, fluoxetine, mirtazapine, paroxetine, sertraline, or venlafaxine) were included in the study. Depression diagnoses were identified using the International Classification of Disease (9th edition) [ICD-9] codes: 296.2x, 296.3x, 296.90, 296.99, 298.0, 300.4, 311, 293.83, 301.12, 309.0, or 309.1. Patients were excluded if they had any of the following diagnoses during the study period: bipolar I, bipolar II, schizophrenia, or schizoaffective disorder.

Study variables

Patients' gender, age, race, ethnicity, and marital status were ascertained from national VA databases. Patients were categorized into four age groups of <40, 40–49, 50–64, and ≥ 65 years based on their age at the first antidepressant. Each patient was classified into one of four racial categories (Black, White, other, or unknown race), and patients' ethnicity was defined as Hispanic or non-Hispanic.

All diagnosis, medication, and utilization data (except suicide attempt) were based on data during the 12 months prior to first new antidepressant start. We obtained diagnoses data for post-traumatic stress disorder (PTSD), personality disorder, major depression, other anxiety disorder, substance-use disorders (either alcohol or other substance abuse or dependence), and tobacco-use disorder. Medical comorbidity was defined as having 0, 1, 2 or ≥ 3 comorbidities

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included in the Charlson Comorbidity Index.[10] Services utilization data were categorized based on their distribution: number of psychiatric stays (0, 1, ≥2), number of outpatient visits (0–3, 4–12, or ≥13), number of outpatient mental health visits (0, 1–2, ≥3) and having had any psychotherapy visits (based on CPT codes). We also obtained Medicare use and the number of psychotropic medications (0, 1, ≥2) prescribed in the 12 months prior to new antidepressant start. The number of psychotropic medications is a count of psychotropic meds received which includes drugs for alcohol treatment, anxiety meds, hypnotics, mood stabilizers, antidepressants, antipsychotics, stimulants, and anticolinesterase medications. Facility variables included geographic region of the country (Northeast, West, Midwest, or South) and location in an urban versus rural area based on Metropolitan Statistical Area designation. Suicide attempts were obtained based on ICD-9 codes E950-E959 and ICD-10 codes X60-X84 and Y87.0 using the data during prior 3 years.[11]

Antidepressant agents

Our primary outcome of interest was choice of antidepressant agent for new antidepressant starts following a 6-month clean period without any antidepressant fills or supply. We assessed new starts of seven of the most commonly prescribed antidepressants, four in the SSRI class (fluoxetine, sertraline, paroxetine, and citalopram), and three dual action alternative antidepressants (venlafaxine, bupropion, and mirtazapine). We did not include older antidepressants such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOI) because they are used far less frequently. The seven antidepressants comprise 90% of the antidepressant prescriptions filled in the VA during the study period. The clean period had to be clean of *all* antidepressants including tricyclics. Time since depression diagnosis to the first antidepressant start was also assessed, with truncation at 2 years.

Data analyses

Descriptive statistics were calculated with percentages for categorical variables and means and standard deviations for continuous variables. Predictors of antidepressant choice were examined using multinomial logistic regression models.[12] To account for potential correlation within facility, we obtained robust standard errors with clustering by facility using Huber/White sandwich estimators.[13] Because much of the variation in choice of antidepressant agent for new starts may be due to small area practice patterns, we conducted a sensitivity analysis, in which a model was fit with facilities included as dummy variables, rather than including the facility-level variables of region and urban facility. All analyses were conducted using Stata10.1 (College Station, TX).

RESULTS

Patient characteristics associated with antidepressant choice

Of the patients diagnosed with depression who initiated a new antidepressant treatment, 502 179 patients started one of the seven antidepressants. Of them, 81 112 patients (16.2%) had at least one other episode of a new antidepressant start. We focused the analyses primarily on the first new antidepressant starts. The majority of the patients were male and non-Hispanic White.

The distribution of the antidepressant agent types is shown by fiscal year in Table 1. Of the seven antidepressants, the majority were given an SSRI: sertraline was prescribed in 27.0% of patients, citalopram in 26.1%, fluoxetine in 14.0%, and paroxetine in 13.3%. Of the non-SSRIs, bupropion was prescribed more often (10.9%) than mirtazapine (4.2%) or venlafaxine (4.4%). Rates of bupriopion prescription remained similar across years, but other antidepressants showed differing prescription trends over the study years. Initial prescriptions of mirtazapine, venlafaxine, and citalopram tended to increase over study years, while prescriptions of sertraline and paroxetine decreased.

Table 2 shows patient characteristics associated with each of the seven antidepressants. Due to the large sample size, the choice of antidepressant had statistically significant associations with many predictor variables. We emphasize those predictors with noticeably different distributions for an antidepressant choice.

We found that bupropion was prescribed less often to older patients; 16% of bupropion fills were for patients ≥65 years compared to 29.5% or more of fills of other antidepressants. Not surprisingly, given its dual indication for depression and smoking cessation, 36.2% of bupropion fills were prescribed to depressed patients with comorbid tobacco use disorder compared to 17.7% or less of fills of other antidepressants. For each antidepressant agent, the proportion of patients with comorbid psychiatric illnesses such as anxiety disorder was substantial; however, a substantially larger proportion of patients receiving

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Table 1. Distribution of seven first antidepressant agents by fiscal year* for the VA patients diagnosed with depression who received at least one prescription to an antidepressant; percents sum to 100% by each fiscal year

New start year	All patients	Serotonin reuptake inhibitor (SSRI)				Non-SSRI		
		Citalopram	Fluoxetine	Paroxetine	Sertraline	Bupropion	Mirtazapine	Venlafaxine
1999†	23 241	2732 (11.8)	4069 (17.5)	3863 (16.6)	8947 (38.5)	2580 (11.1)	413 (1.8)	637 (2.7)
2000	59 841	11 772 (19.7)	8331 (13.9)	9860 (16.5)	19 962 (33.4)	6313 (10.6)	1590 (2.7)	2013 (3.4)
2001	81 553	21 299 (26.1)	9516 (11.7)	11 935 (14.6)	23 898 (29.3)	8843 (10.8)	3026 (3.7)	3036 (3.7)
2002	100 676	31 645 (31.4)	10 658 (10.6)	14 278 (14.2)	25 208 (25.0)	10 241 (10.2)	4506 (4.4)	4140 (4.1)
2003	115 684	32 527 (28.1)	16 907 (14.6)	14 290 (12.4)	28 522 (24.7)	12 338 (10.7)	5447 (4.7)	5653 (4.9)
2004	121 184	31 308 (25.8)	21 018 (17.3)	12 701 (10.5)	29 118 (24.0)	14 377 (11.9)	6165 (5.0)	6497 (5.4)
N (%)	502 179	131 283 (26.1)	70 499 (14.0)	66 927 (13.3)	135 655 (27.0)	54 692 (10.9)	21 147 (4.2)	21 976 (4.4)

*Fiscal year begins on 1 October and ends on 30 September of the following year.
†1999 data were only from mid fiscal year.

mirtazapine or venlafaxine had major depression diagnoses rather than other depressive disorder diagnoses, and a larger proportion of patients receiving mirtazapine had concurrent substance abuse than those receiving fills of other antidepressants. Mirtazapine was also preferentially prescribed to patients with higher levels of concurrent medical conditions, to those with previous psychiatric inpatient hospitalizations, to those with outpatient mental health visits and to those with psychotherapy visits in prior year. Of the four SSRIs, meaningful differences in prescription patterns were seen with age, with SSRI agents other than fluoxetine being filled more often by patients 65 years or older (37% or more of fills compared to 31% of fluoxetine fills). Paroxetine was filled more often by patients with other anxiety disorders (21% of fills) than were other SSRI agents (15% or less of fills).

Covariate adjusted predictors of seven commonly used antidepressant agents

Table 3 gives the relative risk ratios (RRRs) based on the multinomial logistic model predicting antidepressant agent selection, adjusting for facility as well as patient variables listed in the table. Sertraline was the reference category for all RRRs because it had the largest sample size. We emphasize the predictors with RRRs of >2.0 or <0.5, but because indications for the various SSRI agents are potentially more similar, we considered RRRs of close to or <0.75 (or >1.33) to be potentially meaningful predictors of agent choice within the SSRI class.

Patient age and anxiety disorder remained as important patient characteristics associated with the choice of initial antidepressant agent even after adjusting for other variables. Patients with other anxiety disorder diagnoses were 1.68 times (95% CI = 1.64–1.72) more likely to start on paroxetine than sertraline. Relative to younger patients (<40 years), older (≥65 years) patients were 0.37 times (95% CI = 0.35–0.38) less likely to have started on bupropion than sertraline as an initial antidepressant, and of the SSRIs, older patients were 0.70 times (95% CI = 0.67–0.73) less likely to have started on fluoxetine than sertraline. Black patients were less likely to start on paroxetine (RRR = 0.80; 95% CI = 0.77–0.82) than sertraline, while Hispanics were more likely to start on paroxetine than sertraline (RRR = 1.61; 95% CI = 1.54–1.67). We explored whether increased use of paroxetine in Hispanic patients was associated with prior psychotherapy visits or age, and found paroxetine to be used more often in older Hispanics; older Hispanics (≥65 years) were 2.0 times ($p < 0.001$) more likely than younger Hispanics (<40 years) to start on paroxetine than sertraline. Patients with PTSD were also more likely to start on sertraline or mirtazapine than other antidepressants. Patients with tobacco-use disorder were 3.16 times (95% CI = 3.08–3.24) more likely to be prescribed bupropion than sertraline, while no other agents showed notable RRR for tobacco use disorder.

Although unadjusted analyses showed increased use of non-SSRIs than SSRIs in those with psychotherapy in prior year, the differences did not remain after adjusting for covariates. All non-SSRIs were more likely to be filled than sertraline or other SSRIs by those with at least one outpatient mental health visit in the year prior to the index prescription, and in particular, mirtazapine was more likely to be filled than sertraline by 2.93 times in those with one to two visits and 3.68 times in those with at least three visits. On the other hand, patients with 13 or more total outpatient visits were 0.49 times less likely to have started on venlaflaxine than sertraline. Of the SSRIs, fluoxetine and paroxetine, compared with sertraline, were significantly less likely to be prescribed for those with

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Table 2. Patient characteristics by the first antidepressant agent filled[†]

	All patients ($n = 502\,179$)	Serotonin reuptake inhibitor (SSRI)				Non-SSRI		
		Citalopram ($n = 131\,283$)	Fluoxetine ($n = 70\,499$)	Paroxetine ($n = 66\,927$)	Sertraline ($n = 135\,655$)	Bupropion ($n = 54\,692$)	Mirtazapine ($n = 21\,147$)	Venlafaxine ($n = 21\,976$)
Age group (years)								
<40	49 807 (9.9)	12 003 (9.1)	7933 (11.3)	6571 (9.8)	11 662 (8.6)	7109 (13.0)	1797 (8.5)	2732 (12.4)
40–49	84 648 (16.9)	20 963 (16.0)	12 326 (17.5)	10 672 (16.0)	20 109 (14.8)	12 579 (23.0)	3879 (18.3)	4120 (18.8)
50–64	196 669 (39.2)	50 412 (38.4)	28 637 (40.6)	24 562 (36.7)	49 780 (36.7)	26 211 (47.9)	8419 (39.8)	8648 (39.4)
65+	171 055 (34.1)	47 905 (36.5)	21 603 (30.6)	25 122 (37.5)	54 104 (39.9)	8793 (16.1)	7052 (33.4)	6476 (29.5)
Male	460 603 (91.7)	120 702 (91.9)	63 517 (90.1)	61 286 (91.6)	125 324 (92.4)	49 962 (91.4)	20 225 (95.6)	19 587 (89.1)
Female	41 576 (8.3)	10 581 (8.1)	6982 (9.9)	5641 (8.4)	10 331 (7.6)	4730 (8.7)	922 (4.4)	2389 (10.9)
Race								
White	378 850 (75.4)	99 845 (76.1)	52 253 (74.1)	52 415 (78.3)	102 582 (75.6)	39 505 (72.2)	15 197 (71.9)	17 053 (77.6)
Black	64 413 (12.8)	16 435 (12.5)	8711 (12.4)	7144 (10.7)	18 861 (13.9)	7341 (13.4)	3897 (18.9)	1934 (8.8)
Other	10 555 (2.1)	2930 (2.2)	1582 (2.2)	1254 (1.9)	2631 (1.9)	1250 (2.3)	480 (2.3)	428 (2.0)
Unknown	48 361 (9.6)	12 073 (9.2)	7953 (11.3)	6114 (9.1)	11 581 (8.5)	6596 (12.1)	1483 (7.0)	2561 (11.7)
Hispanic	24 653 (4.9)	6548 (5.0)	4115 (5.8)	4398 (6.6)	5796 (4.3)	2148 (3.9)	832 (3.9)	816 (3.7)
SA: Alcohol	60 190 (12.0)	15 102 (11.5)	8208 (11.6)	7278 (10.9)	14 981 (11.0)	8277 (15.1)	4056 (19.2)	2288 (10.4)
SA: Drugs	41 804 (8.3)	10 191 (7.8)	5559 (7.9)	4895 (7.3)	10 116 (7.5)	5984 (10.9)	3326 (15.7)	1733 (7.9)
PTSD	66 494 (13.2)	17 590 (13.4)	8286 (11.8)	7689 (11.5)	17 741 (13.1)	7685 (14.1)	4564 (21.6)	2939 (13.4)
Major depression	104 900 (20.9)	26 992 (20.6)	14 159 (20.1)	12 344 (18.4)	25 154 (18.5)	13 156 (24.1)	6588 (31.2)	6507 (29.6)
Other anxiety disorder	76 547 (15.2)	20 078 (15.3)	8399 (11.9)	14 277 (21.3)	18 933 (14.0)	6900 (12.6)	4098 (19.4)	3862 (17.6)
Personality disorder	10 342 (2.1)	2459 (1.9)	1409 (2.0)	1395 (2.1)	2457 (1.8)	1339 (2.5)	695 (3.3)	588 (2.7)
Tobacco-use disorder	82 701 (16.5)	18 908 (14.4)	9953 (14.1)	8933 (13.4)	18 438 (13.6)	19 774 (36.2)	3743 (17.7)	2952 (13.4)
Suicide attempt	2000 (0.4)	483 (0.4)	242 (0.3)	227 (0.3)	523 (0.4)	229 (0.4)	170 (0.8)	126 (0.6)
No. of Charlson comorbidities								
0	273 435 (54.5)	68 434 (52.1)	41 039 (58.2)	37 502 (56.0)	69 884 (51.5)	32 285 (59.0)	11 091 (52.5)	13 193 (60.0)
1	138 984 (27.7)	36 806 (28.0)	18 711 (26.5)	18 425 (27.5)	38 622 (28.5)	14 910 (27.3)	5770 (27.3)	5740 (26.1)
2	56 654 (11.3)	16 078 (12.3)	7066 (10.0)	7203 (10.8)	16 499 (12.2)	5154 (9.4)	2619 (12.4)	2035 (9.3)
3+	33 106 (6.6)	9965 (7.6)	3683 (5.2)	3790 (5.7)	10 650 (7.9)	2343 (4.3)	1667 (7.9)	1008 (4.6)
No. of psych stays								
0	468 191 (93.2)	122 897 (93.6)	66 342 (94.1)	62 993 (94.1)	126 748 (93.4)	50 814 (92.9)	18 295 (86.5)	20 102 (91.5)
1	25 550 (5.1)	6311 (4.8)	3169 (4.5)	2982 (4.5)	6651 (4.9)	2836 (5.2)	2100 (9.9)	1501 (6.8)
2+	8438 (1.7)	2075 (1.6)	988 (1.4)	952 (1.4)	2256 (1.7)	1042 (1.9)	752 (3.6)	372 (1.7)
No. of outpatient visits								
0–3	158 205 (31.5)	36 711 (28.0)	25 135 (35.7)	24 621 (36.8)	42 532 (31.4)	15 305 (28.0)	5007 (23.7)	8894 (40.5)
4–12	199 032 (39.6)	52 688 (40.1)	27 668 (39.3)	25 853 (38.6)	53 935 (39.8)	22 638 (41.4)	8202 (38.8)	8048 (36.6)
13+	144 942 (28.9)	41 884 (31.9)	17 696 (25.1)	16 453 (24.6)	39 188 (28.9)	16 749 (30.6)	7938 (37.5)	5034 (22.9)
No. of outpatient mental health visits								
0	239 628 (47.7)	62 060 (47.3)	35 442 (53.0)	35 442 (53.0)	71 916 (53.0)	19 677 (36.0)	5182 (24.5)	8718 (39.7)
1–2	170 166 (33.9)	45 580 (34.7)	20 792 (31.1)	20 792 (31.1)	41 648 (30.7)	21 677 (39.6)	9034 (42.7)	8887 (40.4)
3+	92 385 (18.4)	23 643 (18.0)	10 693 (16.0)	10 693 (16.0)	22 091 (16.3)	13 338 (24.4)	6931 (32.8)	4371 (19.9)
No. of psych meds								
0	266 596 (53.1)	68 182 (51.9)	39 750 (56.4)	35 756 (53.4)	74 666 (55.0)	29 200 (53.4)	9070 (42.9)	9972 (45.4)
1	151 125 (30.1)	40 304 (30.7)	20 543 (29.1)	20 294 (30.3)	40 514 (29.9)	15 947 (29.2)	6530 (30.9)	6993 (31.8)
2+	84 458 (16.8)	22 797 (17.4)	10 206 (14.5)	10 877 (16.3)	20 475 (15.1)	9545 (17.5)	5547 (26.2)	5011 (22.8)
Medicare	144 278 (28.7)	38 186 (29.1)	18 447 (26.2)	21 670 (32.4)	44 304 (32.7)	8980 (16.4)	6229 (29.5)	6462 (29.4)
Psychotherapy visit	104 484 (20.8)	26 796 (20.4)	13 067 (18.5)	12 425 (18.6)	25 454 (18.8)	14 915 (27.3)	6946 (32.9)	4881 (22.2)
Region								
Northeast	95 852 (19.1)	22 855 (17.4)	12 870 (18.3)	13 825 (20.7)	28 590 (21.1)	3794 (17.9)	3794 (17.9)	3910 (17.8)
Midwest	112 977 (22.5)	29 060 (22.1)	12 739 (18.1)	15 873 (23.7)	32 079 (23.7)	5845 (27.6)	5845 (27.6)	5164 (23.5)
South	193 540 (38.5)	50 308 (38.3)	26 871 (38.1)	25 204 (37.7)	54 999 (40.5)	7623 (36.1)	7623 (36.1)	8487 (38.6)
West	99 810 (19.9)	29 060 (22.1)	18 019 (25.6)	12 025 (18.0)	19 987 (14.7)	3885 (18.4)	3885 (18.4)	4415 (20.1)
Urban facility	452 354 (90.1)	119 939 (91.4)	63 093 (89.5)	60 305 (90.1)	121 316 (89.4)	48 924 (89.4)	18 944 (89.6)	19 833 (90.2)
Days since diagnosis[*]	10 (448)	5 (403)	4 (407)	7 (406)	5 (354)	73 (715)	71 (730)	26 (453)

Values are all *n* (%), except days since diagnosis which is median (inter-quartile range).
SA, substance abuse; PTSD, post-traumatic stress disorder.
[*]Days since first depression diagnosis (cohort entry) to the first new start of one of seven antidepressant agents, truncated at 730 days.
[†]All variables are significantly different across groups ($p < 0.0001$).

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Table 3. Adjusted relative risk ratios [RRR (95% CI)] for the type of antidepressant agents with sertraline as the reference anti-depressant

	Serotonin reuptake inhibitor (SSRI)			Non-SSRI		
	Citalopram	Fluoxetine	Paroxetine	Bupropion	Mirtazapine	Venlafaxine
Age (vs. <40 years)						
40–49 years	1.02 (0.99–1.05)	0.97 (0.93–1.01)	0.97 (0.94–1.01)	0.94 (0.90–0.98)*	1.11 (1.05–1.18)*	0.99 (0.94–1.05)
50–64 years	0.96 (0.93–0.99)*	0.93 (0.90–0.96)‡	0.93 (0.90–0.97)‡	0.83 (0.80–0.86)‡	1.01 (0.95–1.07)	0.86 (0.82–0.91)‡
65+ years	0.92 (0.89–0.95)‡	0.70 (0.67–0.73)‡	0.83 (0.80–0.87)‡	0.37 (0.35–0.38)‡	1.11 (1.03–1.18)*	0.59 (0.56–0.63)‡
Male (vs. Female)	0.99 (0.96–1.02)	0.89 (0.86–0.92)‡	0.95 (0.92–0.99)*	1.17 (1.12–1.21)‡	1.77 (1.64–1.90)‡	0.80 (0.76–0.84)‡
Race (vs. White)						
Black	0.85 (0.83–0.87)‡	0.86 (0.83–0.88)‡	0.80 (0.77–0.82)‡	0.76 (0.74–0.79)‡	1.11 (1.07–1.16)‡	0.53 (0.50, 0.56)‡
Other	0.99 (0.94–1.05)	0.97 (0.91–1.04)	0.89 (0.83–0.95)*	0.93 (0.87–0.99)*	1.00 (0.90–1.10)	0.83 (0.75, 0.93)*
Unknown	0.93 (0.90–0.96)‡	0.94 (0.91–0.98)*	0.94 (0.91–0.97)*	1.01 (0.97–1.04)	0.86 (0.81–0.91)‡	0.93 (0.88–0.98)*
Hispanic	1.02 (0.98–1.06)	1.25 (1.20–1.31)‡	1.61 (1.54–1.67)‡	0.82 (0.78–0.86)‡	0.78 (0.73–0.85)‡	0.74 (0.69–0.80)‡
Alcohol abuse	1.00 (0.97–1.03)	1.04 (1.00–1.07)*	1.02 (0.98–1.05)	0.79 (0.76–0.82)‡	1.04 (0.98–1.09)	0.76 (0.72–0.80)‡
Drug abuse	0.98 (0.94–1.01)	1.06 (1.01–1.11)*	1.08 (1.03–1.13)*	0.98 (0.94–1.02)	1.19 (1.11–1.26)‡	0.93 (0.87–0.99)*
PTSD	0.87 (0.85–0.89)‡	0.76 (0.73–0.78)‡	0.83 (0.81–0.86)‡	0.65 (0.63–0.67)‡	0.99 (0.95–1.03)	0.70 (0.67–0.74)‡
Major depression	1.07 (1.04–1.09)‡	1.08 (1.05–1.11)‡	0.98 (0.96–1.01)	1.06 (1.04–1.09)‡	1.36 (1.32–1.41)‡	1.53 (1.48–1.59)‡
Other anxiety disorder	1.05 (1.03–1.08)‡	0.84 (0.82–0.86)‡	1.68 (1.64–1.72)‡	0.73 (0.71–0.75)‡	1.12 (1.08–1.17)‡	1.08 (1.04–1.12)‡
Personality disorder	0.99 (0.93–1.05)	1.11 (1.03–1.19)*	1.14 (1.07–1.23)‡	0.93 (0.86–0.99)*	0.97 (0.89–1.07)	1.11 (1.01–1.22)*
Tobacco-use disorder	1.00 (0.97–1.02)	1.00 (0.98–1.03)	1.02 (0.99–1.05)	3.16 (3.08–3.24)‡	1.06 (1.02–1.11)*	0.97 (0.93–1.01)
Suicide attempt	0.90 (0.80–1.03)	0.83 (0.71–0.97)*	0.90 (0.76–1.05)	0.80 (0.68–0.94)*	1.09 (0.90–1.31)	1.01 (0.83–1.24)
No. of Charlson Comorbidities						
1 (vs. none)	0.98 (0.96–0.99)*	0.92 (0.90–0.94)‡	0.95 (0.93–0.97)‡	0.94 (0.92–0.97)‡	0.94 (0.90–0.97)‡	0.95 (0.92–0.99)*
2 (vs. none)	0.99 (0.96–1.01)	0.87 (0.84–0.89)‡	0.91 (0.88–0.94)‡	0.82 (0.79–0.86)‡	0.96 (0.92–1.01)	0.87 (0.83–0.92)‡
3+ (vs. none)	0.95 (0.92–0.98)*	0.75 (0.71–0.78)‡	0.78 (0.74–0.81)‡	0.64 (0.61–0.68)‡	0.95 (0.89–1.01)	0.74 (0.69–0.80)‡
No. of psych inpatient stays						
1 (vs. none)	0.98 (0.94–1.02)	0.84 (0.80–0.88)‡	0.86 (0.82–0.91)‡	0.74 (0.70–0.78)‡	1.39 (1.30–1.48)‡	1.30 (1.21–1.39)‡
2+ (vs. none)	0.96 (0.90–1.03)	0.81 (0.74–0.88)‡	0.84 (0.77–0.91)‡	0.65 (0.60–0.71)‡	1.16 (1.05–1.29)*	1.16 (1.03–1.32)*
No. of outpatient visits						
4–12 (vs. 0–3)	1.10 (1.08–1.12)‡	0.85 (0.83–0.87)‡	0.80 (0.78–0.82)‡	0.91 (0.89–0.94)‡	0.91 (0.87–0.94)‡	0.61 (0.59–0.63)‡
13+ (vs. 0–3)	1.21 (1.18–1.24)‡	0.79 (0.77–0.81)‡	0.70 (0.68–0.72)‡	0.88 (0.85–0.91)‡	0.94 (0.89–0.98)*	0.49 (0.47–0.52)‡
No. of outpatient mental health visits						
1–2 (vs. none)	1.29 (1.27–1.32)‡	1.04 (1.01–1.06)*	0.99 (0.97–1.01)	1.80 (1.75–1.85)‡	2.93 (2.81–3.05)‡	1.69 (1.63–1.76)‡
3+ (vs. none)	1.24 (1.20–1.29)‡	1.06 (1.02–1.11)‡	0.99 (0.95–1.04)	1.92 (1.84–2.01)‡	3.68 (3.47–3.91)‡	1.98 (1.86–2.11)‡
No. of other psychotropic medications						
1 (vs. 0)	1.06 (1.05–1.08)‡	1.01 (0.99–1.03)	1.02 (1.00–1.05)*	0.95 (0.93–0.97)‡	1.05 (1.02–1.09)*	1.27 (1.23–1.32)‡
2+ (vs. 0)	1.15 (1.13–1.18)‡	1.05 (1.02–1.08)‡	1.08 (1.05–1.12)‡	1.03 (0.99–1.06)	1.43 (1.38–1.49)‡	1.82 (1.75–1.90)‡
Psychotherapy	0.94 (0.91–0.97)‡	1.01 (0.98–1.04)	1.01 (0.98–1.05)	1.03 (1.00–1.07)*	0.90 (0.86–0.94)‡	0.97 (0.93–1.02)
Medicare use	0.92 (0.90–0.95)‡	0.98 (0.95–1.00)	1.09 (1.06–1.12)‡	0.90 (0.87–0.93)‡	1.13 (1.09–1.18)‡	1.29 (1.24–1.35)‡
Region (vs. West)						
Northeast	0.56 (0.55–0.58)‡	0.52 (0.51–0.54)‡	0.81 (0.79–0.84)‡	0.63 (0.60–0.65)‡	0.64 (0.61–0.67)‡	0.63 (0.60–0.67)‡
Central	0.64 (0.63–0.66)‡	0.45 (0.44–0.46)‡	0.82 (0.79–0.84)‡	0.63 (0.61–0.65)‡	0.95 (0.91–0.99)*	0.73 (0.69–0.76)‡
South	0.64 (0.62–0.65)‡	0.55 (0.53–0.56)‡	0.75 (0.72–0.77)‡	0.62 (0.60–0.64)‡	0.74 (0.71–0.77)‡	0.73 (0.70–0.76)‡
Urban facility	1.22 (1.19–1.25)‡	0.98 (0.95–1.01)	1.10 (1.06–1.13)‡	1.04 (1.01–1.08)*	0.99 (0.94–1.04)	1.13 (1.08–1.19)‡
Fiscal year of new start						
2000 (vs. 1999)	1.98 (1.89–2.08)‡	0.92 (0.88–0.97)*	1.13 (1.08–1.18)‡	1.12 (1.06–1.18)‡	1.83 (1.64–2.05)‡	1.47 (1.34–1.61)‡
2001 (vs. 1999)	3.11 (2.97–3.26)‡	0.88 (0.84–0.92)‡	1.13 (1.09–1.19)‡	1.33 (1.27–1.40)‡	3.23 (2.90–3.59)‡	1.96 (1.79–2.14)‡
2002 (vs. 1999)	4.45 (4.25–4.66)‡	0.94 (0.90–0.98)*	1.28 (1.23–1.34)‡	1.44 (1.37–1.52)‡	4.80 (4.32–5.33)‡	2.62 (2.40–2.86)‡
2003 (vs. 1999)	4.07 (3.89–4.26)‡	1.31 (1.26–1.37)‡	1.14 (1.10–1.19)‡	1.49 (1.41–1.56)‡	5.28 (4.76–5.86)‡	3.27 (3.00–3.56)‡
2004 (vs. 1999)	3.80 (3.63–3.98)‡	1.59 (1.52–1.66)‡	1.00 (0.96–1.04)	1.59 (1.51–1.67)‡	5.76 (5.20–6.39)‡	3.68 (3.38–4.01)‡
Days since diagnosis†	0.99 (0.99–0.99)‡	1.01 (1.01–1.02)‡	1.02 (1.02–1.02)‡	1.08 (1.07–1.08)‡	1.04 (1.04–1.05)‡	1.02 (1.02–1.03)‡

PTSD, post traumatic stress disorder.
†Days (in 100 day units) since first depression diagnosis (cohort entry) to first new start of one of the seven antidepressant agents.
*$p < 0.05$; ‡$p < 0.001$.

three or more comorbid conditions (RRR = 0.75 for fluoxetine and 0.78 for paroxetine) or for those with 13 or more outpatient visits in the year prior to the index prescription (RRR = 0.79 for fluoxetine and 0.70 for paroxetine compared to sertraline).

Significant variation across geographic regions and fiscal year remained after adjusting for patient demographics and other covariates. For regional and yearly variation, we note variation with an RRR <0.75 (or >1.33). Compared with the western region, all other regions were less likely to prescribe bupropion and venlafaxine than sertraline, and the northeast region was less likely to prescribe mirtazapine than sertraline. Of the SSRIs, compared with the Western

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region, all other regions were significantly less likely to prescribe citalopram and fluoxetine than sertraline. Although not markedly different, urban facilities were more likely to prescribe citalopram (RRR = 1.22; 95% CI = 1.19–1.25) than sertraline. Lastly, the choice of SSRI agent varied significantly by year after adjusting for covariates, with mirtazapine, venlafaxine and citalopram more likely to be prescribed toward later years than sertraline. However, when separate models were fit by each fiscal year, factors associated with initial choice of antidepressants, including variation associated with region of the facility, remained similar across years as shown by similar estimates of RRRs especially for those with clinically meaningful and statistically significant associations.

DISCUSSION

We found several patient characteristics to be strongly associated with choice of antidepressant for first new starts after adjusting for potential variation due to facility variables. Among the seven most commonly prescribed antidepressants, patients who had a new start of mirtazapine had a higher burden of psychiatric illness, patients prescribed sertraline were more likely to be over 65 years of age, and patients prescribed paroxetine were more likely to have a comorbid anxiety disorder. These patient characteristics have also been associated with depression outcomes, including suicide risk.[14–16] In addition, as expected, due to its dual indication for depression and cessation of smoking, patients prescribed bupropion had a higher rate of tobacco use disorder.

In patients with mental health visits, non-SSRIs were used more frequently than SSRIs as the initial choice of antidepressant treatment. This could be due either to increased severity of the underlying depressive disorder or that psychiatrists prefer first-line use of non-SSRIs. Though we cannot tell this apart based on the administrative data, increased uses of mirtazapine and venlafaxine were associated with other measures of increased severity, including major depression or number of psychotropic medications. And days since depression diagnosis to new start of an antidepressant were longer for non-SSRIs than SSRIs. These suggest that mirtazapine and venlafaxine are not likely the psychiatrists' preferred first line of antidepressants, but rather their use is associated with increased severity of depression.

SSRIs are generally thought to have similar indications and effectiveness[8,9]; however, patient characteristics were associated with selection of the four SSRIs as well. Elderly patients were less likely to start on fluoxetine than other SSRIs compared with younger patients. This may be due to the greater number of known drug–drug interactions with fluoxetine compared with sertraline or citalopram. Elderly patients may also be less likely to receive fluoxetine because of clinicians' concerns about its long half life, and the possibility of higher medication blood levels over time if it is taken regularly but metabolized more slowly.[14] Paroxetine was more likely to be used in patients with anxiety. Association of antidepressant choice with these patient factors is a concern when using observational data to assess the effectiveness or adverse effects of different treatments. For example, anxiety has been shown to be associated with suicide,[15,16] and if paroxetine were more likely to be prescribed to patients with anxiety, this may result in a potentially misleading conclusion of paroxetine being more likely to be associated with suicide than other SSRIs.

There was considerable regional variation in the antidepressant prescription pattern, even among the four SSRIs and after adjusting for patient characteristics reflecting potential illness severity. Citalopram and fluoxetine, compared with sertraline, were significantly more likely to be prescribed in the Western region. In addition, urban facilities were more likely to prescribe citalopram than sertraline. This reflects variations in regional practices, but also suggests that if different SSRIs were associated with differences in patient outcomes or different tolerability in certain patient subgroups, further standardizing practices across regions might improve care.

While this study offers a nationally representative longitudinal cohort of depressed VA patients, there are several important limitations. The study involves VA patients, of which about 90% are male. In the general population, females represent a large proportion of antidepressant drug users. Though we have no reason to believe that the observed relationships between patient characteristics and the choices of antidepressants in this population would be different in the general population or in the female population, the results need to be verified. Because we used administrative data, we lacked potential key variables that may explain variation in practice patterns, such as costs of antidepressants and provider characteristics. However, because of generous VA pharmacy coverage, cost may be less of a factor in antidepressant choice in the VA than in many other settings. We also did not have information on distant prior antidepressant use that may have been a factor in the antidepressant selection, if patients told prescribing physicians of their previous experiences with a particular agent. Lastly, the study is

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limited to seven antidepressants and four SSRIs, though these seven agents make up 90% of the antidepressant prescriptions at the VA.

Our results highlight the importance of addressing selection bias when conducting comparative studies of antidepressants using observational pharmacoepidemiologic data. Several patient factors are shown to be associated with variation in initial antidepressant choice for VA patients newly treated for depression, including factors which are associated with poorer patient treatment outcomes such as age and concurrent anxiety disorder. In particular, we find the increased use of paroxetine in patients with comorbid anxiety. Our study also showed bupropion to be associated with tobacco addiction. Studies may find bupropion to be associated with decreased risks when this could be due to its use for smoking cessation in those with mild depression. The association between potential predictors of patient outcomes and the choice of an agent seen even among the four most commonly prescribed SSRIs further emphases the importance of controlling for selection bias not only when making comparisons between SSRIs and non-SSRIs, but even within a drug class. Controlling for potential biases is inherently more difficult in observational studies and in particular with studies using administrative data because the data are not collected for research purposes and thus underreporting of potential covariates of the study can be common. For future studies examining antidepressant use and various outcomes using observational data, particular attention needs to be paid to the strong predictors of antidepressant initiation shown in our study. Study results also suggest that reducing regional variation in antidepressant prescribing practices may be a potential area of quality improvement within the VA.

KEY POINTS

- Choice of new antidepressant medication for depressed VA patients was associated with patient characteristics predictive of treatment outcomes, including psychiatric illness severity, age, and likelihood of a comorbid anxiety disorder.
- It is important to control for selection bias when using observational data to compare risks from or effect of mental health treatments associated with antidepressant agents.
- Regional variation in the antidepressant choice is substantial in the depressed VA patients.

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