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14. ABSTRACT

We have completed all Year 2 tasks by the time of this report. We identified which Veterans in the final cohort received an adequate medication trial (AMT) of one of the five medications (fluoxetine, sertraline, paroxetine, topiramate, or venlafaxine) during their initial year of PTSD treatment. We then determined whether each Veteran also received pre- and post-measurement with the PTSD Checklist (PCL) as well as whether they met criteria for PTSD. We have developed our analytic dataset for the completion of Aims 1 and 2, and have also published or submitted three additional manuscripts supporting the methods to be used as we complete our efforts.

15. SUBJECT TERMS

Posttraumatic stress disorder
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INTRODUCTION

Exposure to traumatic events, which is commonly experienced by military service members, can lead to the development of posttraumatic stress disorder (PTSD). Using randomized controlled trials, researchers have identified five medications that consistently appear to treat PTSD: Zoloft® (sertraline), Paxil® (paroxetine), Prozac® (fluoxetine), Effexor® (venlafaxine), and Topamax® (topiramate). However, there are no randomized trials comparing the effects of these five medications in a single patient population. A logical and efficient approach to determine which medications may be most effective for Veterans who use the VA would be to leverage historical treatment data to compare the recommended psychotropic medications for PTSD. All five of these medications have been available and regularly prescribed in the VA for over 15 years, and the VA has a national data warehouse containing information from electronic medical records used in routine practice. In the short term, this research would help Veterans with posttraumatic stress by providing additional information about which medications work the best for their symptoms, and even tailor their choice based on their own unique situation. It would also help VA doctors by giving them additional information about how to best help their patients. In the long term, this research would help Veterans, VA doctors, and researchers by developing a way to learn from clinical practice and incorporate those findings to improve care for posttraumatic stress disorder.

KEYWORDS

Posttraumatic stress disorder
Psychotropic medications
Comparative effectiveness research
Retrospective cohort
Routine practice
Veterans

ACCOMPLISHMENTS

WHAT WERE THE MAJOR GOALS OF THE PROJECT?

The overarching objective of this project is to determine the comparative effectiveness of psychotropic medications to treat PTSD among Veterans in routine clinical practice. There are four aims total, three of which address changes in symptoms associated with an adequate trial of an effective psychotropic medication for PTSD. For the entire cohort, we will evaluate both changes in overall symptoms and changes in specific clusters of symptoms. For smaller clinically important subgroups, we will examine changes in overall symptoms only. The final aim addresses a functional outcome by assessing acute psychiatric care use for the entire cohort following receipt of an adequate trial of an effective psychotropic medication for PTSD.

In order to accomplish these aims, we needed to update and merge existing data and datasets from the VA. With this new cohort, we will develop psychotropic medication receipt variables, such as determining the number of Veterans to receive an adequate medication trial (AMT) of one or more of the five medications of interest and aligning these AMTs with available patient-reported outcome measurement.

Our statement of work (SOW) is divided into four main tasks:

Task 1. Update and Merge Existing Data and Datasets—100% completed
Task 2. Develop Psychotropic Medication Receipt Variables—100% completed

Task 3. Data Analysis—30% completed
Task 4. Finalize study requirements, prepare for future funding, and dissemination of findings—15% completed

Our SOW called for the completion of Task 2 and part of Task 3 by the end of Year 2. Progress on subtasks is described in detail below.

WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

Year 2 Objectives

2. Develop psychotropic medication receipt variables
   a. Determine whether each Veteran in the final cohort received an adequate medication trial (AMT) of fluoxetine, sertraline, paroxetine, topiramate, venlafaxine during their initial year of VA PTSD treatment. (Q5 deliverable)
   b. Determine whether each Veteran who received an AMT also received pre- and post-measurement with the PTSD Checklist (PCL). (Q6 deliverable)
   c. Determine whether each Veteran who received an AMT plus pre/post-measurement meets symptomatic criteria for PTSD by examining individual PCL items. (Q7 deliverable)
3. Data Analysis
   a. Create matched analytic cohorts using a propensity score matching approach. This will include an overall matched cohort and matched cohorts for each of 13 clinically important subgroups. (Q8 deliverable)

As shown in Table 1 below, we have identified the number of VHA users in our cohort have received an AMT of each of the five psychotropic medications used to treat PTSD (**subtask 2a**), aligned these AMTs with PCL measurement (**subtask 2b**), and determined data availability for clinically important subgroups (**subtask 3a**). As shown in Table 2 below, we have also developed and finalized our covariates for propensity score matching (**subtask 3a**).

There have been some challenges and the development of solutions in our task to determine whether Veterans meet symptomatic criteria for PTSD (**subtask 2c)**, as our period of observation overlaps with the transition from the forth to fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV to DSM-V). The process of updating the related PCL tool in the VA EMR resulted in a drop in the availability of structured PCL data between Fiscal Year 14 (FY14) and FY16. Fortunately, through our work on another DoD-funded project (JW140056, PI Maguen), we were able to access a natural language processing (NLP)-based algorithm to fill in this gap using PCL values recorded in clinical note text. While we do have a crosswalk developed by the National Center for PTSD to rescore PCL-IV total scores to the PCL-5 scale, it is not possible to crosswalk individual items given both that the number of symptoms has changed and that total scores extracted from note text using NLP are accompanied by information regarding individual item responses. Thus, across data sources (structured and NLP) and PCL versions, there were over 10 thousand AMTs with PCL measurement (total scores) within two weeks of medication start and within two weeks of week 12 (our AMT period includes a minimum of 8 weeks at adequate dose, with four weeks permitted for medication titration). This included 2,664 AMTs of fluoxetine, 3,577 AMTs of sertraline, 1,332 AMTs of paroxetine, 842 AMTs of topiramate, and 1,714 AMTs of venlafaxine.

Given that multiple aims require examination of individual PCL items (to determine diagnostic criteria at baseline or to determine changes in cluster scores and sleep items), and that the PCL-5 reflects the current diagnostic

criteria for PTSD, we have created an analytic dataset containing the 1,401 AMTs aligned with structured PCL-5 data (389 fluoxetine, 512 sertraline, 145 paroxetine, 151 topiramate, and 204 venlafaxine). This dataset, which categorizes patients as to whether they meet symptomatic and severity criteria for PTSD at baseline (**subtask 2c**) and contains all covariates required for propensity score matching (**subtask 3a**), was transferred from the development phase (data management team) to the analytic phase (analytic team) in September 2019. This will allow us to complete **Aim 1** (comparison of acute phase changes in PTSD symptom outcomes), **Aim 2** (comparison of follow-up phase acute psychiatric care use), and **Aim 3** (examination of changes in cluster scores and sleep items) during **Year 3**, with adequate power to detect a small to medium differences in effect size between agents. However, we will need to use the complete dataset of total scores, cross walked to PCL-5 scoring, to complete **Aim 4** (examination of acute phase changes in PTSD symptoms for clinically important subgroups). This larger dataset will also be used to repeat **Aim 1** and **Aim 2** analyses with power to detect small differences. The notable limitation of these analyses is that we will be required to use a cutoff score of 31-33 on the PCL-5 scale for inclusion rather than assessing symptomatic criteria using individual item scores.

Table 1. Adequate Medication Trials with Pre/Post Data Availability.

	PCL for DSM-IV		PCL for DSM-5		
	PCL-IV Structured	PCL-IV NLP	PCL-5 Structured	PCL-5 NLP	PCL Total
Overall					
Fluoxetine	1,609	306	389	76	2,664
Sertraline	2,253	370	512	112	3,577
Paroxetine	900	135	145	34	1,332
Topiramate	453	102	151	40	842
Venlafaxine	1,107	171	204	61	1,714
Female Gender					
Fluoxetine	193	46	66	16	376
Sertraline	182	40	67	10	336
Paroxetine	83	22	13	4	142
Topiramate	78	18	42	11	175
Venlafaxine	124	24	31	10	210
White Non-Hispanic					
Fluoxetine	1,061	209	235	48	1,757
Sertraline	1,422	260	321	68	2,300
Paroxetine	631	86	96	18	914
Topiramate	309	62	80	22	536
Venlafaxine	785	126	134	35	1,206
Black Non-Hispanic					
Fluoxetine	213	47	66	15	380
Sertraline	368	57	89	26	593
Paroxetine	121	26	24	13	205
Topiramate	68	17	37	8	153
Venlafaxine	124	16	29	8	197
Hispanic					
Fluoxetine	200	41	58	6	334
Sertraline	301	29	62	12	430
Paroxetine	95	15	15	2	136
Topiramate	44	13	22	6	90
Venlafaxine	127	16	28	9	196
OEF/OIF/OND Veteran					

Fluoxetine	1,304	198	268	56	1,972
Sertraline	1,770	226	359	69	2,555
Paroxetine	741	81	107	20	992
Topiramate	397	73	107	23	650
Venlafaxine	878	117	149	51	1,280
Vietnam Veteran					
Fluoxetine	77	24	13	5	159
Sertraline	118	39	20	5	245
Paroxetine	43	9	4	2	78
Topiramate	5	4	0	3	20
Venlafaxine	56	10	4	1	98
Combat Exposure					
Fluoxetine	1,288	196	192	45	1,869
Sertraline	1,764	226	258	45	2,422
Paroxetine	738	81	83	20	971
Topiramate	388	70	79	14	594
Venlafaxine	882	111	103	35	1,215
Military-Related Sexual Trauma					
Fluoxetine	182	46	69	13	367
Sertraline	183	51	63	11	359
Paroxetine	89	17	15	4	143
Topiramate	68	17	38	8	155
Venlafaxine	125	33	29	8	226
Pain Disorder Diagnosis					
Fluoxetine	1,254	239	311	57	2,092
Sertraline	1,804	284	412	93	2,860
Paroxetine	748	102	120	25	1,088
Topiramate	391	88	140	38	738
Venlafaxine	918	140	168	60	1,435
Headache Disorder Diagnosis					
Fluoxetine	712	113	122	19	1,062
Sertraline	954	120	159	30	1,370
Paroxetine	398	55	47	12	558
Topiramate	360	76	101	30	643
Venlafaxine	566	80	66	28	809
Psychotic Disorder Diagnosis					
Fluoxetine	60	10	9	4	94
Sertraline	80	16	11	0	121
Paroxetine	27	4	2	2	36
Topiramate	20	4	3	2	29
Venlafaxine	56	8	2	2	73
Bipolar Disorder Diagnosis					
Fluoxetine	74	13	18	6	127
Sertraline	101	29	27	4	174
Paroxetine	54	10	10	3	84
Topiramate	51	14	17	7	97
Venlafaxine	68	8	12	4	100
Depressive Disorder Diagnosis					
Fluoxetine	1,251	245	312	53	2,095
Sertraline	1,731	294	405	88	2,780
Paroxetine	675	110	107	27	1,013
Topiramate	360	85	127	31	679
Venlafaxine	927	150	178	51	1,446
Anxiety Disorder Diagnosis					

Fluoxetine	756	160	195	35	1,287
Sertraline	1,024	193	267	54	1,709
Paroxetine	442	75	74	26	680
Topiramate	226	58	78	20	429
Venlafaxine	546	108	97	31	877
History of Traumatic Brain Injury					
Fluoxetine	405	63	60	12	568
Sertraline	569	66	73	13	755
Paroxetine	270	22	20	4	322
Topiramate	214	38	30	6	307
Venlafaxine	319	41	37	14	436
Alcohol Use Disorder Diagnosis					
Fluoxetine	550	96	120	30	894
Sertraline	757	129	155	31	1,181
Paroxetine	296	49	39	17	431
Topiramate	146	43	58	13	296
Venlafaxine	405	69	87	27	653
Opioid Use Disorder Diagnosis					
Fluoxetine	79	26	36	6	160
Sertraline	93	24	27	11	170
Paroxetine	50	7	5	0	68
Topiramate	16	5	17	3	51
Venlafaxine	59	19	17	4	111
Other Substance Use Disorder Diagnosis					
Fluoxetine	301	59	86	17	519
Sertraline	402	74	89	21	645
Paroxetine	173	29	25	11	260
Topiramate	73	17	39	10	158
Venlafaxine	224	37	50	9	352

Note. Patients were selected for this cohort based on having a VHA PTSD diagnosis between October 1, 2014 and March 7, 2018. Once patients were included in this cohort, their records were examined back to October 1, 1999; PCL=PTSD Checklist; DSM=Diagnostic and Statistical Manual of Mental Disorders; NLP=Natural Language Processing

Table 2. Characteristics of Adequate Medication Trials with Measurement (n=10,129).

Trial Characteristics	
Number of Measured Trials Patients Contribute	
1, %(n)	95.6 (9,253)
2, %(n)	4.2 (409)
3+, %(n)	0.2 (19)
Number of Prior Adequate EBM trials (with or without PCL)	
0, %(n)	80.3 (8,132)
1, %(n)	15.8 (1,601)
2+, %(n)	3.9 (396)
Number of Prior Adequate EBP Trials (with or without PCL)	
0, %(n)	94.9 (9,614)
1, %(n)	4.9 (493)
2+, %(n)	0.2 (22)

Acute Psychiatric Services in 6 Months after Follow-Up PCL	
ED Visits for Psychiatric Indications, % (n)	7.6 (770)
Inpatient Psychiatric Hospitalization (Any), % (n)	5.3 (538)
Days from Qualifying PTSD Diagnosis to Baseline PCL, M (SD)	818.0 (1,139.3)
Days from Baseline PCL to Follow-Up PCL, M (SD)	82.4 (16.9)
Concurrent Treatment	
Any PE, %, n	6.3 (641)
Sessions of PE, M, SD	4.5 (2.9)
Any Individual CPT, %, n	18.7 (1,893)
Sessions of Individual CPT, M, SD	4.7 (3.2)
Any Group CPT, %, n	7.5 (761)
Sessions of Group CPT, M, SD	5.4 (4.6)
Any Non-EBP Individual Therapy, %, n	59.9 (6,071)
Any Non-EBP Group Therapy, %, n	29.3 (2,970)
Any Non-EBM Antidepressant, %, n	55.3 (5,599)
Any Non-Topiramate Anticonvulsant, %, n	25.9 (2,624)
Any Sedative/Hypnotics, %, n	31.8 (3,216)
Any Opioid, %, n	19.4 (1,968)
Any Atypical Antipsychotic, %, n	18.7 (1,891)
Any Prazosin, %, n	37.4 (3,792)
Any Naltrexone or Acamprosate, %, n	2.7 (277)
Any Opioid Replacement Therapy, %, n	1.8 (185)
Primary Prescribing Clinician Characteristics	
Age, M (SD)	50.1 (11.3)
Women, % (n)	40.9 (4,145)
Psychiatrist, % (n)	44.5 (4,509)
Other Physician, % (n)	27.2 (2,751)
Physician Assistant, % (n)	5.0 (502)
Nurse Practitioner, % (n)	19.3 (1,955)
Pharmacist, % (n)	3.2 (326)
Percentage of Time Seeing PTSD Patients in Various Settings	
PTSD Service Section (PCT or residential), M (SD)	12.6 (28.0)
Substance Abuse Service Section, M (SD)	3.0 (11.7)
Comorbid PTSD Substance Abuse Service Section, M (SD)	0.0 (0.8)
General Mental Health Service Section, M (SD)	83.6 (33.6)
Integrated Care Service Section, M (SD)	6.5 (18.2)
Primary Care Service Section, M (SD)	30.9 (2.3)
Patient Characteristics at Baseline	
Age, M (SD)	39.8 (12.1)
Women, % (n)	12.2 (1,239)
Married, % (n)	58.1 (5,880)
Rural, % (n)	41.4 (4,197)
White Non-Hispanic, % (n)	66.3 (6,713)
Black Non-Hispanic, % (n)	15.1 (1,528)
Hispanic, % (n)	11.7 (1,186)
OEF/OIF/OND Veteran, % (n)	73.5 (7,449)
Vietnam Veteran, % (n)	5.9 (600)
Combat Exposure, % (n)	69.8 (7,071)
Sexual Trauma while in Military, % (n)	12.3 (1,250)
VA Disability Level 70% or Greater, % (n)	54.0 (5,467)

Service Use Characteristics in the 1 Year Preceding Baseline	
Any PTSD Outpatient Clinical Team Visits, % (n)	38.5 (3,902)
Number of PTSD Outpatient Clinical Team Visits, M (SD)	11.6 (17.7)
Any Outpatient Mental Health Visits, % (n)	87.9 (8,902)
Number of Outpatient Mental Health Visits, M (SD)	25.4 (45.3)
Any Outpatient Substance Abuse Visits, % (n)	14.1 (1,432)
Number of Outpatient Substance Abuse Visits, M (SD)	25.7 (43.5)
Any Outpatient Primary Care Visits, % (n)	81.8 (8,288)
Number of Outpatient Primary Care Visits, M (SD)	5.4 (5.6)
Any ED Visits for Psychiatric Indication, % (n)	15.0 (1,523)
Number of ED Visit for Psychiatric Indication, M (SD)	1.7 (1.5)
Any Acute Inpatient Mental Health Treatment, % (n)	12.9 (1,309)
Days of Acute Inpatient Mental Health, M (SD)	21.9 (35.4)
Any Residential PTSD Treatment, % (n)	2.5 (252)
Days Residential PTSD Treatment, M (SD)	33.6 (33.6)
Any Residential Substance Abuse Treatment, %(n)	2.5 (256))
Days Residential Substance Abuse Treatment, M (SD)	36.3 (34.5)
Comorbidities in the 2 Years Preceding Baseline	
Pain Disorder, % (n)	81.1 (8,213)
Headache Disorder, % (n)	43.9 (4,442)
Psychotic Disorders, % (n)	3.5 (353)
Bipolar Mood Disorders, % (n)	5.8 (582)
Depressive Mood Disorders, % (n)	79.1 (8,013)
Anxiety Disorders, %(n)	49.2 (4,982)
Traumatic Brain Injury, % (n)	23.6 (2,388)
Alcohol Use Disorders, % (n)	34.1 (3,455)
Opioid Use Disorders, % (n)	5.5 (560)
Other Substance Use Disorders, % (n)	19.1 (1,934)

Note. Patients are selected for this table based on meeting our PCL-based measurement criteria (see Table 1). EBM=evidence-based medication, including fluoxetine, sertraline, topiramate, paroxetine, or venlafaxine; EBP=Evidence-Based Psychotherapy, including prolonged exposure (PE), cognitive processing therapy delivered in individual (CPT-I) and group (CPT-G) formats; ED=Emergency Department; PCT=PTSD Care Team

Other Achievements

To support future extensions of our work, we have begun to merge other important data sources into our study cohort. This year, we received IRB approval for the the addition of: 1) Veterans Access, Choice, and Accountability Act (VACAA) and Centers for Medicare and Medicaid Services (CMS) files; 2) VA/DoD Suicide Data Repository (SDR) files; 3) DoD-VA Infrastructure for Clinical Intelligence (DaVINCI); and 4) Suicide Prevention Applications Network (SPAN) data. We have initiated required data use agreements. These data sources will support future work examining whether evidence-based PTSD treatments decrease suicide risk, and whether other medications in addition to the five we are studying could be helpful in decreasing PTSD symptoms. Our initial proposal on PTSD treatment and suicide risk was submitted to the DoD Joint Warfighter Medical Research Program (JWMRP) in August 2018. This spring, we learned that proposal, entitled "Evaluating the Effect PTSD and Evidence-Based PTSD Treatment on Death by Suicide" received a high score and was chosen as an alternate for funding. While the proposal was eventually not chosen, we have submitted a letter of intent to submit an improved proposal to JWMRP. Our initial proposal on examining

additional medications for potential effectiveness in treating PTSD was submitted to the National Institutes of Mental Health special solicitation on VA/DoD data in February 2019. This summer, we learned that the proposal, entitled "Identification of Novel Agents to Treat PTSD using Clinical Data" scored at the 16th percentile and is under consideration for funding without a required resubmission. We will receive a final determination this fall.

Goals Not Met

As discussed above, we have not yet finalized our larger analytic dataset for **Aim 4**. Through the process of data summarization for our Year 2 report, we learned that **the cohort identifiers provided to us by the VA Informatics and Computing Infrastructure (VINCI) included only VHA users with a diagnosis of PTSD from the start of FY 2015 through March 7, 2018.** We were provided data on these Veterans back to FY1999 to account for prior treatment history. **The cohort should have included all VHA users with a diagnosis of PTSD dating back to FY1999.** This mistake was made due to an older process by VINCI data stewards, since corrected, whereby they would cut and paste cohort selection criteria from one project to another and would not provide cohort selection code for study teams to verify. Because the current version of our patient-reported outcome measure, the PCL-5, was not introduced as a structured variable in the VA EMR until FY2015, the incorrect dates used by VINCI for cohort selection do not interfere with our ability to complete Aims 1-3: as discussed above, our current analytic dataset aligns 1,401 AMTs with structured PCL-5 data and will provide adequate sample size to detect small to medium differences between the five agents. However, also as discussed above, **we will need to crosswalk total scores on the older and newer version of the PCL to have adequate power to complete Aim 4 subgroup analyses**, and to detect small differences between agents in Aims 1 and 2. **As currently constructed, our cohort includes the older version of the PCL only on VHA users who continued to have PTSD after the start of FY2015 (i.e. those that did not get better). To avoid selection bias for PCL crosswalk, we will have to correct the cohort to include VHA users with a new diagnosis of PTSD between FY1999-FY2019.** This date range will ensure that we capture all AMTs with aligned PCL measurement and prior treatment history back to the time the era that the five agents became available in the VA. Work to re-develop the overall cohort will be completed during Year 3 while analyses for Aims 1-3 are completed using the currently-available analytic dataset containing structured PCL-5 data. After finalization of the overall analytic data set, we will request a no-cost extension if related analyses cannot be completed by the end of Year 3.

WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

Nothing to report.

HOW WERE THE RESULTS DISSEMINATED TO COMMUNITIES OF INTEREST?

Using Dr. Shiner's pilot cohort, developed for his VA HSR&D career development award (CDA), we developed an array-based method of aligning medication dosing, symptomatic measurement, and other treatment events such as concurrent evidence-based psychotherapy for PTSD. This has allowed us to better align the timing our outcome measurements with medication treatment. In addition to using this method to develop the study cohort described in Tables 1 and 2, we submitted two manuscripts for publication using the pilot cohort. First, "Using Patient-Reported Outcomes to Understand the Effectiveness of Guideline-Concordant Care for Posttraumatic Stress Disorder in Clinical Practice" formed the basis for our improved alignment of patient-reporting outcomes and treatment receipt. Second,

"Measurement Strategies for Evidence-Based Medications for Posttraumatic Stress Disorder Delivery: Trends and Associations with Patient-Reported Outcomes" built on this work by adding the medication dosing and titration algorithms used to develop our study cohort.

WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

We are completely confident that we will complete Aims 1-3 using our current analytic cohort during Year 3. We are also completely confident that we will concurrently expand our analytic cohort for the increased sample size required for Aim 4 (and to detect small difference between agents in Aims 1 and 2) during Year 3. While we hope to start on analyses for Aim 4 during Year 3, we may need to request a 1-year no cost extension to allow enough time to complete analyses for Aim 4.

IMPACT

WHAT WAS THE IMPACT ON THE DEVELOPMENT OF THE PRINCIPAL DISCIPLINE(S) OF THE PROJECT?

Our major contributions to the principal discipline of the project are highlighted in our two manuscript submissions. In "Using Patient-Reported Outcomes to Understand the Effectiveness of Guideline-Concordant Care for Posttraumatic Stress Disorder in Clinical Practice" we characterize treatments received by patients with regular PCL measurements. Patients who receive regular PCL measurements in clinical practice also receive high levels of evidence-based treatments for PTSD, including both medications and psychotherapy. Thus, our approach to leveraging PCL measurements is appropriate for comparing outcomes among those who receive evidence-based treatments, but may not be appropriate for comparing those who do and do not receive evidence-based treatments. Fortunately, this is consistent with the strategy we have chosen in this project. In "Measurement Strategies for Evidence-Based Medications for Posttraumatic Stress Disorder Delivery: Trends and Associations with Patient-Reported Outcomes," we outline our approach to identify patients who initiate an adequate trial of an evidence-based medication for PTSD in clinical practice. While this work clearly supports our strategy to identify cases for inclusion in analyses for this project, it also shows that the vast majority of VA patients receiving medication treatment for PTSD receive medications that are not effective for PTSD or medications that are effective but prescribed at an inadequate dose, for an inadequate duration, or without adequate follow-up. Thus, work to develop the analytic cohort for this project has identified a major opportunity for improvement in VA PTSD treatment. Co-Investigator Watts, now the VA's Executive Director of Systems Redesign and Improvement, is developing a VA HSR&D proposal that will compare various implementation strategies to address poor prescribing.

WHAT WAS THE IMPACT ON OTHER DISCIPLINES?

Nothing to report.

WHAT WAS THE IMPACT ON TECHNOLOGY TRANSFER?

Nothing to report.

WHAT WAS THE IMPACT ON SOCIETY BEYOND SCIENCE AND TECHNOLOGY?

Nothing to report.

CHANGES/PROBLEMS

CHANGES IN APPROACH AND REASONS FOR CHANGE

As discussed above, VINCI provided us with all VHA users with new PTSD episodes between FY2015 through the April 2018. While this selection will be ideal for completion of Aims 1-3 during Year 3, we will now also have to update the cohort during Year 3 to include the complete timeframe (FY1999-2019) to have adequate power to complete Aim 4. As discussed above, we are confident that we will be able to complete Aims 1-3, as well as update the cohort for Aim 4 during Year 3. However, we may need to request a no-cost extension to complete analyses for Aim 4.

ACTUAL OR ANTICIPATED PROBLEMS OR DELAYS AND ACTIONS OR PLANS TO RESOLVE THEM

Due to the cohort selection error with VINCI, we anticipate needing to request a no-cost extension for one additional year to complete data analysis for Aim 4, as well as dissemination of findings.

CHANGES THAT HAD A SIGNIFICANT IMPACT ON EXPENDITURES

Nothing to report.

SIGNIFICANT CHANGES IN USE OR CARE OF HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS

Nothing to report.

PRODUCTS

PUBLICATIONS, CONFERENCE PAPERS, AND PRESENTATIONS

Journal publications

Shiner B, Leonard Westgate C, Gui J, Maguen S, Young-Xu Y, Schnurr PP, Watts BV. (2018). A Retrospective Comparative Effectiveness Study of Medications for Posttraumatic Stress Disorder in Routine Practice. Journal of Clinical Psychiatry, 79(5):18m12145. Status: Published; Acknowledgement of federal support: Yes.

Shiner B, Gui J, Leonard Westgate C, Schnurr PP, Watts BV, Cornelius SL, Maguen S. (2019). Using patient-reported outcomes to understand the effectiveness of guideline-concordant care for post-traumatic stress disorder in clinical practice. Journal of Evaluation in Clinical Practice, 25(4): 689-699. Status: Published. Acknowledgement of federal support: Yes.

Shiner B, Leonard Westgate C, Gui J, Cornelius S, Gradus JL, Schnurr PP, Watts BV. (2019). Measurement Strategies for Evidence-Based Antidepressants for Posttraumatic Stress Disorder Delivery: Trends and Associations with Patient-Reported Outcomes. Administration and Policy in Mental Health and Mental Health Services Research. Status: Under Review. Acknowledgement of federal support: Yes.

Books or other non-periodical, one-time publications

Nothing to report.

Other publications, conference papers, and presentations

Nothing to report

WEBSITE(S) OR OTHER INTERNET SITE(S)

Nothing to report

TECHNOLOGIES OR TECHNIQUES

Nothing to report

INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Nothing to report

OTHER PRODUCTS

Nothing to report

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Brian Shiner, MD, MPH (Principal Investigator): No change.
Paula P. Schnurr, PhD (Co-Investigator): No change.
Bradley V. Watts, MD, MPH (Co-Investigator): No change.
Yinong Young-Xu, DSc (Co-Investigator): No change.
Jiang Gui, PhD (Co-Investigator): No change.
Christine Westgate, MS (Lead Programmer): No change.
Vincent Dufort, PhD (Programmer): No change.
Daniel Gottlieb, MS (Programmer): No change.
Sarah Cornelius, BS (Research Assistant): No change.

HAS THERE BEEN A CHANGE IN THE ACTIVE OTHER SUPPORT OF THE PD/PI(S) OR SENIOR/KEY PERSONNEL SINCE THE LAST REPORTING PERIOD?

Dr. Shiner's VA HSR&D Career Development Award (CDA) ended in June 2019. Because this eliminates the potential for overlap, key personnel including Drs. Shiner, Watts, and Schnurr will use grant funds for salary support during Year 3.

WHAT OTHER ORGANIZATIONS WERE INVOLVED AS PARTNERS?

Nothing to report for Year 2. For Year 3, we have begun Joint Personnel Agreements with our academic affiliate (Dartmouth) for Drs. Shiner, Watts, and Schnurr. This will allow study funds to be used for salary support now that Dr. Shiner's CDA is over.

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS

Not applicable to this project

QUAD CHARTS

Not applicable to this project

APPENDICES

We have attached the final versions of the two manuscripts published thus far, as well as the page proofs of the third manuscript under review.

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A Retrospective Comparative Effectiveness Study of Medications for Posttraumatic Stress Disorder in Routine Practice

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National Center for Patient Safety, Ann Arbor, MI, and Assistant Professor of Psychiatry, Geisel School of Medicine, Hanover, NH

Abstract

Objective: Fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine have consistently shown efficacy for posttraumatic stress disorder (PTSD) in metaanalyses of randomized controlled trials. However, no study has compared the effectiveness of these agents in routine clinical practice. We conducted a retrospective comparative effectiveness study of these five medications using electronic medical record data.

Method: We identified 2,931 Department of Veterans Affairs outpatients initiating treatment for PTSD between fiscal years 2004 and 2013 who received one of the five medications at an adequate

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Previous Presentations: None

dose and duration, combined with baseline and endpoint PTSD checklist (PCL) measurements. Patients were identified based on clinical diagnoses of PTSD. We weighted participants in order to balance pretreatment characteristics. We compared continuous changes on total PCL score, symptom cluster scores, and sleep items, as well as categorical changes including reliable improvement and loss of PTSD diagnosis using weighted regression analyses. We conducted exploratory analysis to determine whether any patient characteristics or service use variables predicted loss of PTSD diagnosis.

Results: Patients improved by a mean of 5–6 points on the PCL over approximately six months of treatment. While half of patients had a reliable improvement of 5 points or more on the PCL, less than a fifth achieved loss of PTSD diagnosis. There were no differences between medications. The only significant predictor of loss of PTSD diagnosis was concurrent treatment with evidence-based psychotherapy.

Conclusion: Available evidence-based medications for PTSD are equally effective in clinical practice. Although effective, our data suggest that patients choosing medication treatment for PTSD should consider concurrent treatment with evidence-based psychotherapy in order to maximize their chances of meaningful improvement.

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a serious condition that can follow exposure to a traumatic event, characterized by intrusive re-experiencing of the trauma in the form of flashbacks and nightmares, avoidance of trauma reminders, negative alterations in cognitions and mood, and increased arousal and reactivity.[1] PTSD has a lifetime prevalence of almost 8% in the United States.[2] Over 10% of Veterans receiving care in the Department of Veterans Affairs (VA) health care system have PTSD, and the VA has a caseload of almost 600,000 Veterans receiving PTSD treatment.[3]

Randomized controlled trials (RCTs) show that effective treatments for PTSD include both pharmacologic and psychotherapeutic approaches.[4,5] There have been multiple meta-analyses examining the effectiveness of medications to treat PTSD, which have differed in their methods and conclusions. Watts et al.'s meta-analyses of all RCTs of PTSD treatment conducted through 2012 showed results consistently favoring four antidepressants (fluoxetine, paroxetine, sertraline, and venlafaxine), one anticonvulsant (topiramate), and one antipsychotic (risperidone) when compared directly to placebo.[5] A similar review by Hoskins et al. favored fluoxetine, paroxetine, and venlafaxine, but not sertraline, topiramate, or risperidone.[6] A meta-analysis by Lee et al. that included RCTs of medications for PTSD published through 2015 suggested superior efficacy for sertraline, venlafaxine, and nefazodone compared to other medications.[7] Two studies used network meta-analysis to make indirect comparisons between medications.[8] First, a 2013 Agency for Healthcare Research and Quality (AHRQ) network meta-analysis of published RCTs concluded that paroxetine and topiramate were most effective, but that fluoxetine, sertraline, and venlafaxine were also effective.[4] Second, Cipriani et al. concluded that phenelzine was superior to other medications for PTSD when considering both efficacy and dropouts.[9] Data supporting the phenelzine finding came from one small RCT,[10] and Cipriani et al. called for further study rather than prioritizing phenelzine in clinical practice.[9] Given available data,

the preponderance of metaanalyses suggest fluoxetine, sertraline, paroxetine, topiramate, and venlafaxine as treatments for PTSD.

While several medications have demonstrated efficacy for PTSD in clinical trials, there have been few head-to-head comparisons and no large trials. Furthermore, while multiple medications for PTSD have shown superiority to placebo in RCTs, little is known about their effectiveness in routine clinical practice. There are several reasons to question whether medications found efficacious in highly controlled clinical studies are beneficial in typical clinical practice. First, patients with comorbidities such as substance abuse are common in the population,[11] yet are routinely excluded from efficacy trials of PTSD treatments.[12] Second, RCTs of psychotropic medications for PTSD typically prohibit patients from undergoing concurrent psychotherapy,[5] whereas these interventions are often delivered together in practice.[13] Given advancements in data, including increasing availability of patient reported outcome data in the electronic medical record (EMR) ,[14] and the need for large numbers to support research on more personalized medicine,[15] observational studies are a logical extension of CER research on psychotropic medications for PTSD.

We conducted a retrospective comparative effectiveness study of medications for PTSD using VA EMR data. We examined medications already determined as effective for PTSD in multiple meta-analyses, including fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine. Based on the AHRQ network meta-analytic results, we expected that participants receiving paroxetine and topiramate might have superior symptomatic outcomes. However, given limitations both about the applicability of RCT results to the clinical population and the relatively limited evidence for topiramate, it was not possible to make a formal prediction. We elected not to examine medications whose efficacy was supported in a single meta-analysis or single study since, in most cases, these medications have been used too infrequently in VA practice to yield reliable results.[16] Lastly, we examined predictors of response to medication treatment generally as well as to each of the agents individually.

Method

Data Sources

We used the VA Corporate Data Warehouse (CDW) to identify VA users with new PTSD treatment episodes from fiscal years 2004 through 2013 and obtain information on services use, clinical diagnoses, pharmacy data, and standardized measures of PTSD symptoms. This study was approved by the Veterans Institutional Review Board (IRB) of Northern New England, which is the IRB of record for the White River Junction VAMC. .

Participants

Participants were drawn from a large retrospective cohort of VA users with new PTSD treatment episodes between fiscal years 2004 and 2013 that has been described elsewhere.[11,17] This parent cohort included VA users who received a primary diagnosis of PTSD at two or more outpatient encounters, at least one of which occurred in a mental health setting, over the course of 90 days.[18,19] Participants meeting this criterion during the prior two years were

excluded. We examined one year of treatment receipt following the first encounter with a qualifying diagnosis of PTSD. The study sample was further restricted to those who had an adequate medication trial (AMT, defined below), received baseline PTSD symptom measurement at the start of treatment (up to two months prior and two weeks after the start of an AMT), and received follow-up PTSD symptom measurement (greater than eight weeks and less than six months after initiating an AMT). To minimize heterogeneity and confounding, participants who received two or more AMTs concurrently were excluded. When patients had two or more AMTs sequentially, we examined only the first. Due to increasing use of standardized measurement of PTSD symptoms in clinical practice in more recent years,[20,21] participants in this analysis were treated in fiscal year 2008 and later.

PTSD Symptoms

We measured PTSD symptoms using the PTSD Checklist (PCL), which is administered in clinical practice and recorded in the VA EMR. During the time period we examined, the VA used the version of the PCL corresponding to PTSD diagnostic criteria in the fourth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).[22,23] The PCL is a 17-item measure with each item rated on a five-point Likert-type scale with total scores ranging from 17 through 85. Minimal symptomatic criteria for PTSD using the PCL include 1 re-experiencing symptom, 3 avoidance and numbing symptoms, and 2 hyperarousal symptoms, all rated “moderately” or higher. Participants are asked to rate symptoms over the last month. Previous research in Veterans shows that a change of five points cannot be attributed to measurement error,[24] so we used a five-point drop as our threshold for reliable improvement. A meaningful change in PTSD symptoms plus no longer meeting diagnostic criteria for PTSD has been shown to be an important marker of improved quality of life.[25] Therefore we also employed no longer meeting DSM-IV criteria for PTSD as measured by the PCL, plus a clinically meaningful drop of 10 points,[26] as our threshold for loss of diagnosis.

In addition to examining overall change in symptoms, we evaluated change in sub-scores for PTSD symptoms clusters as well as sleep difficulties using the sum of two items: nightmares and insomnia. Diagnostic criteria for PTSD changed in May 2013 with the publication of DSM-5.[1] A key change in the criteria is replacement of the “avoidance and numbing cluster” with “avoidance” and “negative alterations in cognitions and mood” clusters. To approximate this distinction, we divided “avoidance” and “numbing” symptoms. Our symptom clusters consisted of five reexperiencing items, two avoidance items, five emotional numbing items, and five hyperarousal items.

Psychotropic Medication Receipt

We developed algorithms to measure whether participants received an AMT of sertraline, fluoxetine, paroxetine, venlafaxine, or topiramate, defined as eight weeks of a daily dose at least as high as the dose used in the efficacy trials supporting the treatment recommendation.[4,5] While the length of efficacy trials of psychotropic medications for PTSD varies, the VA practice guideline in use during the time period we examined recommended medication trials of at least eight weeks.[27] Therefore, participants receiving continuous treatment of one of the following medications daily for eight weeks or more were considered to have received

an AMT: fluoxetine 20 mg or more daily, paroxetine 20 mg or more daily, sertraline 100 mg or more daily, topiramate 100 mg or more daily, and venlafaxine 150 mg or more daily.

Independent Variables

Participant variables included demographics, military service characteristics, commonly occurring medical and mental health disorders, and baseline PCL score. Health system variables included the type of VA facility and the prescribing clinician's service section. Service use characteristics during the year following the index PTSD diagnosis included concurrent psychotropic medication, total number of psychotherapy encounters, number of psychotherapy encounters where participants received evidence-based psychotherapy (EBP) for PTSD, defined as prolonged exposure (PE)[28] or cognitive processing therapy (CPT),[29] and counts of medication management encounters, primary care encounters, and outpatient visits. We measured PE and CPT use with a natural language processing (NLP) algorithm that classifies psychotherapy notes in individual (I) and group (G) delivery formats.[30] In our pilot NLP work, we attempted to identify other evidence based psychotherapies for PTSD including Eye Movement Desensitization and Reprocessing (EMDR) and Stress Inoculation Therapy (SIT).[31] Despite manual review of over 7,500 notes written about patients attending PTSD clinics, we were unable to detect any examples of these therapies in routine clinical practice in VA. Therefore, their use was not included in further analysis steps.

Analysis

To understand how participants selected for this analysis differed from the rest of the parent cohort during the relevant fiscal years, we compared patient characteristics using χ^2 analysis and t-tests, as appropriate. We compared these same characteristics among participants who received each of the five medications within the smaller analytic cohort using pairwise testing with step-down Bonferroni-adjusted p-values.

To account for baseline differences among participants who received each of the five medications, we used the RAND Toolkit for Weighting and Analysis of Nonequivalent Groups (TWANG).[32] The TWANG package supports causal modeling of observational data through the estimation and evaluation of propensity scores and associated weights. In our application, the propensity score represented the probability that a particular patient would receive each medication.[33] We estimated propensity scores with multinomial logistic regression using generalized booster effects,[34] in which the dependent variable is an indicator for each psychotropic medication and the independent variables are an anti-parsimonious specification of variables that have a plausible correlation with the outcome.[33,34] Using these propensity scores, we weighted participants in order to balance the pretreatment covariate distributions.

We compared continuous and categorical outcomes among the five groups with regression analyses using psychotropic medication received as the sole independent variable. In general, weighted means can have greater sampling variance than unweighted means. Therefore, we used survey commands, which account for the weights, to perform the outcomes analyses when comparing the weighted groups. For continuous outcomes, we used linear regression analysis, whereby the coefficient of the variable tests the hypothesis that

each of the five psychotropic medications has the same mean change in PTSD symptoms. For categorical outcomes, we used logistic regression analysis, whereby the coefficient of the variable tests the hypothesis that each of the five psychotropic medications results in the same percentage of patients achieving reliable improvement or loss of PTSD diagnosis. Finally, we conducted exploratory univariate logistic regression analyses to determine whether any independent variables predicted achievement of our categorical response criteria of loss of PTSD diagnosis by pooling all five groups together and using the unweighted data. Because there were 50 independent variables, we used a Bonferroni-corrected value of $p<0.001$ for significance in these exploratory analyses. Analyses were performed using R, Version 3.2.0.

Results

While 29.0% (142,276) of 491,040 VA users meeting our criteria for a new episode of PTSD care between fiscal years 2008 and 2013 had a qualifying medication trial, only 0.6% (2,931) also received outcome measurement within our specified time frames. The 2,931 participants included in our analyses differed from patients with AMT who did not have PCL measurement in almost every measurable way in terms of demographics, service use, comorbidity, or concurrent medication use (Table 1). Many of these differences were statistically significant but of unclear clinical relevance. In some ways the analytic sample differed in ways that were likely clinically meaningful. Most notably, compared to the general population with PTSD, the analytic sample contained younger participates (on average 8 years younger) more likely to be Operations Enduring Freedom/Iraqi Freedom/New Dawn (OEF/OIF/OND) Veterans (69.2% vs. 34.9%), with higher rates VA disability (68.2% vs. 55.6%). The analytic sample also differed in important ways regarding their mental health services use: they were more likely to receive medications from a mental health clinician (86.7% vs. 38.3%), had more individual psychotherapy visits (mean of 16.2 vs. 6.6), and more likely to receive group psychotherapy (61.9% vs. 34.8%).

The number of participants in the analytic cohort receiving each medication ranged from 1,376 who received sertraline to 105 who received topiramate (Table 2). The number of eligible participants grew across treatment years, with the majority of participants in the analytic sample treated in fiscal years 2012 and 2013. While there were notable differences among the medication treatment groups, our weighting procedure allowed us to balance almost all covariates (Table 2, Table 3). The exception was whether baseline PCL occurred during medication titration period. For medications that commonly require a lengthier titration period – sertraline, topiramate, and venlafaxine – baseline PCL score occurred during the titration period more often than for fluoxetine and paroxetine, where both treatments generally start at full dose. We did not further adjust for this difference because it is more likely related to medication characteristics than to participant characteristics. The mean AMT length was 254.1 (SD=119.5) days when including continuation of treatment beyond the index year. Relative to the start of the AMT, participants' baseline PCLs were administered at 9.7 (SD=11.8) days prior to the start of the AMT and end-point PCLs were administered a 174.7 (SD=99.5) days after the start of the AMT. In the unweighted model, mean baseline PCL scores indicated a high burden of symptoms, ranging from 61.5 to 62.5 (Table 2, Table 4).

All five of the medications that were studied demonstrated a significant effect on PTSD symptoms. The mean improvement in PTSD symptoms measured by the PCL scores ranged from 5.0 to 6.3 points, indicating statistically reliable but modest improvements; between 41.9% and 52.9% of participants achieved a an improvement of 5 points or more. As inclusion in the cohort was based on encounter-based diagnostic information (2 PTSD diagnoses within 90 days, at least one of which was in a mental health clinic), 12.4% (n=363) patients did not meet PCL-based diagnostic criteria at baseline. However, there were no overall or pairwise differences among agents at baseline. Among those who met PCL-based diagnostic criteria for PTSD at baseline, between 13.6% and 20.4% of participants achieved our threshold for loss of diagnosis, an outcome associated with substantial clinical improvement. As measured by the PCL, there was a very limited range of baseline PTSD symptom clusters and sleep item scores and changes on these scores. There were no significant differences between medications in any outcome using the unweighted model. Weighted model adjusting for differences between the medication treatment groups was very similar to the unadjusted analysis and there continued to be no differences in outcomes (Table 5), meaning that the five medications performed about equally in reducing PTSD symptoms, even after adjusting for differences between treatment groups.

In our exploratory univariate logistic regression models, the only significant ($p<0.001$) patient-level predictors of loss of diagnosis were related to receipt of EBP for PTSD, including PE and CPT, delivered in an individual format (EBT-I). Across all treatment groups, the number of sessions of EBT-I during the index year of treatment predicted improvement (OR=1.07), and the effect was greater if the sessions occurred during the AMT (OR baseline-midpoint=1.14; OR midpoint-end=1.13). There were four predictors not achieving the of loss of PTSD diagnosis, including TBI and other cognitive disorders (OR=0.65), male gender (OR=0.63), OEF/OIF/OND Veteran status (OR=0.71), and non-psychotherapy mental health visits (OR=0.98). No additional variables or patterns of variables emerged as predictors of response when examining participants who received individual medications.

Discussion

We compared the effectiveness of five evidence-based medications for PTSD in routine clinical practice and found that they performed similarly. During an average of six months of treatment, participants experienced a five- to six-point improvement in PCL scores. Approximately half of participants achieved a reliable improvement of five points or more on the PCL. Our findings are consistent with meta-analytic findings that have suggested that fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine are effective treatments for PTSD.[4,5] However, less than a fifth of participants achieved our more stringent improvement criterion: loss of PTSD diagnosis. None of the medications led to superior outcomes in individual PTSD symptom clusters or sleep items.

The only independent variables that predicted loss of PTSD diagnosis were related to concurrent treatment with EBP-I for PTSD. Therefore, while fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine appear to be equally effective in clinical practice, our findings do not support the idea that patient characteristics can guide the selection of the

medication most likely to be effective.[35] Instead, it appears that there is clinical equipoise and the choice of individual agent should be up to patients who elect to take a medication for PTSD.[36] However, to maximize improvement, patients should also be encouraged to consider concurrent EBP-I. Prior analysis in the parent cohort from which this analytic sample was derived demonstrated that men and OEF/OIF/OND Veterans are less likely to complete psychotherapy for PTSD.[37] While studies have clearly demonstrated that patients with TBI can tolerate and benefit from evidence-based PTSD treatment,[38–41] this evidence is largely derived from specialized residential settings and may not generalize to the outpatient care studied in this analysis. Thus, it is not particularly surprising that men, OEF/OIF/OND Veterans, and those with a history of TBI or other cognitive disorders had poorer treatment outcomes given the importance of concurrent EBP-I. That more non-psychotherapy mental health visits are also a negative predictor of treatment response is not surprising, as these visits may indicate that participants had a greater variety of mental health treatment needs and comorbid mental health conditions.

There are several major limitations to our study. First, participants meeting inclusion criteria for our analytic cohort differed from the general VA PTSD treatment population in many ways. The patient sample in the analysis were younger, more likely veterans of recent wars, and received more mental health services. Because of this it is unclear if these findings generalize to older veterans of earlier service eras receiving less mental health services. Moreover, we have no clear understanding of whether these finds would apply to non-veterans with PTSD in general. Second, were unable to measure all related aspects of care. As an example, we could not measure medication adherence or psychotherapy protocols that are less frequently in the VA such as EMDR. However, the mean length of treatment was six months, indicating that participants typically exhausted their initial fill (which can last up to 90 days) and requested refills. Lastly, we only considered PTSD outcomes. Depression and quality of life measures were not available, but they may have enriched our exclusive focus on PTSD outcomes.

While we found that all of the medication treatments for PTSD that we studied were effective in clinical practice, their effect seemed reduced compared to that seen in the clinical trials. Such comparisons are difficult to make precisely in all cases because various studies use different measures and allowed various concurrent treatments. However, as an example Berlant et al.'s open-label study of topiramate for PTSD and found a mean change in PCL scores of 21 points (we found a 5-point change) and 34% with loss of diagnosis (we found 16%).[42] The reasons for possible reduction in effectiveness are unknown. One possibility is that drug trials have more stringent criteria for inclusion, subsequently not generalizing to the typical veteran population seen in clinic (e.g., no substance use disorders, suicidality, etc.). It is also possible that VA patients are more treatment-resistant than patients enrolling in RCTs. Future work using our methods should attempt to examine patients' treatment history longitudinally rather than cross-sectionally to address this concern.

We conclude that available evidence-based medications for PTSD are equally effective in clinical practice. Although effective, our data suggest that patients choosing medication

treatment for PTSD should consider concurrent treatment with EBP-I for PTSD in order to maximize their chances of meaningful improvement.

Clinical Points:

-Five medications for PTSD with consistent efficacy in metaanalyses of randomized controlled trials—including fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine—are also effective in routine clinical practice.

-It does not appear that any one of these agents is more effective than the others for PTSD, so patient preference should weigh heavily when choosing among these medications.

-Patients who elect to take one of these mediations for PTSD should consider undergoing concurrent treatment with evidence-based psychotherapy delivered in an individual format, such as prolonged exposure or cognitive processing therapy.

Additional Information:

The VA Corporate Data Warehouse (CDW) contains electronic medical record data compiled from individual VA facilities and is described at http://www.hsrd.research.va.gov/for_researchers/vinci/cdw.cfm. Data are stored on geographically dispersed server farms. To access the CDW, researchers generally need to have an employment relationship with the VA. After local institutional review board approval, requests for data are submitted to VA National Data Systems using the Data Access Request Tracker. Datasets are then built and analyzed in secure virtual project workspaces within the VA Informatics and Computing Infrastructure environment. Researchers with VA network access can obtain descriptions of CDW data at http://vaww.virec.research.va.gov/.

Podcast Text:

In this study, which used the treatment records of all patients treated in the Veterans Health Administration over more than a decade, authors determined that five medications that had been shown effective to treat PTSD in research studies also appear to work in real world clinical use. The medications fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine all led to improvements in PTSD symptoms. The medications were about equally effective. It did appear that using any of these medications combined with evidence based psychotherapy for PTSD led to the greatest benefit for patients with PTSD.

Disclosures and acknowledgements:

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Table 1:

VA Users with New Episodes of PTSD Care from 2008 to 2013, by Receipt of an Adequate Trial of an Effective Mediation for PTSD and by Availability of Time-constrained Outcome Measurement as Measured with the PTSD Checklist

	Overall (491,040)	Qualifying Trial 29.0% (142,276)	Plus Measurement 0.6% (2,931)
Demographic Characteristics			
Age, M (SD)	48.5 (16.0)	48.4 (15.1) **	40.2 (12.8) ##
Men, % (n)	90.7 (445,583)	89.5 (127,282) **	87.9 (2,577) #
Married, % (n)	52.7 (258,764)	54.2 (77,177) **	56.6 (1,660) #
White Non-Hispanic, % (n)	63.5 (311,756)	65.5 (93,154) **	64.0 (1,876) #
Black Non-Hispanic, % (n)	19.1 (93,666)	18.1 (25,799) **	16.7 (490)
Hispanic, % (n)	8.1 (39,827)	7.9 (11,303) *	11.1 (322) ##
OEF/OIF/OND Veteran, % (n)	34.9 (171,364)	33.9 (48,228) **	69.2 (2,028) ##
Rural, % (n)	35.0 (171,644)	36.7 (52,202) **	35.0 (1,025) #
Homeless, % (n)	5.4 (26,574)	5.8 (8,295) **	5.0 (148)
Combat Exposure, % (n)	28.6 (140,344)	27.7 (39,458) **	28.8 (845)
Sexual Trauma while in Military, % (n)	9.3 (45,803)	10.6 (15,091) **	12.4 (362) #
VA Disability Level 70 or greater, % (n)	55.6 (273,242)	60.4 (85,925) **	68.2 (1,998) ##
Service Use Characteristics			
Plurality of Care at a VA Medical Center, % (n)	60.4 (296,563)	60.5 (86,069)	65.4 (1,916) ##
Plurality of Care at a Community Based Outreach Clinic, % (n)	30.8 (151,106)	30.6 (43,585)	23.4 (686) ##
Medication was from a primary care prescriber, % (n)	4.2 (20,436)	8.8 (12,671) **	7.4 (216) #
Medication was from a mental health prescriber, % (n)	38.3 (187,999)	84.6 (120,387) **	86.7 (2,541) ##
Primary Care Visits, M (SD)	3.3 (3.2)	3.6 (3.3) **	3.7 (3.0)
Any Individual Psychotherapy, % (n)	86.5 (424,983)	89.8 (127,761) **	98.5 (2,886) ##
All Individual Psychotherapy Visits, M (SD)	6.5 (7.9)	7.6 (8.6) **	16.2 (11.6) ##
Individual Evidence Based Therapy Sessions, M (SD)	0.6 (2.3)	0.6 (2.3)	3.4 (5.0) ##
Has any Group Psychotherapy, % (n)	34.8 (170,816)	36.9 (52,478) **	61.9 (1,815) ##
All Group Psychotherapy Visits, M (SD)	5.2 (15.5)	6.2 (17.5) **	13.7 (26.6) ##
Group Cognitive Processing Therapy, M (SD)	0.6 (2.6)	0.7 (2.7) **	2.4 (4.6) ##
Other Mental Health Visits, M (SD)	8.5 (10.1)	10.6 (10.8) **	15.4 (13.8) ##
Substance Abuse/Detox Visits, M (SD)	1.8 (11.1)	2.2 (12.1) **	3.8 (16.4) ##

	Overall (491,040)	Qualifying Trial 29.0% (142,276)	Plus Measurement 0.6% (2,931)
Comorbid Diagnoses			
Pain Disorder, % (n)	64.9 (318,802)	69.4 (98,764) **	76.0 (2,228) ##
Headache Disorder, % (n)	25.1 (123,441)	28.8 (40,922) **	41.8 (1,224) ##
Psychotic Disorders, % (n)	4.2 (20,682)	4.7 (6,748) **	3.5 (102) ##
Bipolar Mood Disorders, % (n)	6.2 (30,560)	6.5 (9,223) **	5.8 (169)
Depressive Mood Disorders, % (n)	60.3 (296,071)	71.4 (101,557) **	79.6 (2,332) ##
Non-PTSD Anxiety Disorders, % (n)	28.5 (139,779)	33.0 (46,940) **	43.2 (1,267) ##
Traumatic Brain Injury and Cognitive Disorders, % (n)	13.4 (65,834)	14.7 (20,882) **	27.3 (799) ##
Personality Disorders, % (n)	3.9 (18,959)	4.8 (6,873) **	5.0 (148)
Nicotine Dependence, % (n)	39.0 (191,712)	41.9 (59,659) **	44.3 (1,299) #
Alcohol Dependence, % (n)	22.6 (111,027)	24.2 (34,485) **	30.0 (880) ##
Marijuana Dependence, % (n)	3.2 (15,586)	3.6 (5,094) **	4.8 (141) #
Opioid Dependence, % (n)	3.2 (15,903)	3.8 (5,436) **	4.4 (129)
Concurrent Medication Use			
Other Antidepressant, % (n)	63.3 (310,685)	63.5 (90,308)	69.6 (2,041) ##
Other Anticonvulsant, % (n)	24.4 (119,808)	30.1 (42,867) **	34.0 (996) ##
Lithium, % (n)	1.4 (6,848)	1.5 (2,152) **	2.1 (60) #
Antipsychotic, % (n)	20.3 (99,698)	26.8 (38,173) **	27.7 (813)
Sedative/Hypnotics, % (n)	39.6 (194,681)	49.1 (69,886) **	52.8 (1,548) #
Opioids, % (n)	37.0 (181,788)	42.7 (60,687) **	41.0 (1,203) #
Prazosin, % (n)	18.6 (91,543)	25.2 (35,842) **	43.8 (1,285) ##
Stimulants, % (n)	2.5 (12,521)	3.2 (4,482) **	4.4 (129) ##

Note. PTSD=Posttraumatic Stress Disorder, M=mean, SD=standard deviation, OEF/OIF/OND=Operations Enduring Freedom/Iraqi Freedom/New Dawn, VA= Department of Veterans Affairs

* p<0.05

** p<0.001 for Overall versus those with a Qualifying Trial

# p<0.05

p<0.001 for those with a Qualifying Trial with versus without Measurement

Table 2:

Participants with an Adequate Trial of an Effective Medication for PTSD plus Outcomes Measurement, 2008–2013 (Unweighted)

Agent	Fluoxetine	Paroxetine	Sertraline	Topiramate	Venlafaxine	
Total Number	659	328	1,376	105	463	Pairwise Differences
Index Year FY08–9, % (n)	7.1 (47)	7.6 (25)	5.2 (72)	7.6 (8)	5.4 (25)	
Index Year FY10–11, % (n)	32.5 (214)	33.2 (109)	34.0 (468)	41.9 (44)	33.0 (153)	
Index Year FY12–13, % (n)	60.4 (398)	59.1 (194)	60.8 (836)	50.5 (53)	61.6 (285)	
Baseline Symptoms and Alignment of Medication Initiation and Baseline Measurement						
Baseline PCL Score, M (SD)	61.8 (11.8)	62.2 (12.1)	62.0 (11.7)	61.5 (12.6)	62.5 (12.0)	No Differences
Baseline PCL Score before initiation, % (n)	50.7 (334)	50.0 (164)	36.9 (508)	35.2 (37)	29.6 (137)	F≠STV, P≠SV, S≠V
Baseline PCL Score during titration, % (n)	7.1 (47)	7.9 (26)	24.6 (338)	23.8 (25)	18.4 (85)	FP≠STV
Baseline PCL Score full dose, % (n)	42.2 (278)	42.1 (138)	38.5 (530)	41.0 (43)	52.1 (241)	FS≠V
						Demographic Characteristics
Age, M (SD)	39.4 (12.4)	38.7 (13.2)	41.0 (13.2)	38.7 (10.8)	40.2 (12.1)	P≠S
Men, % (n)	88.0 (580)	87.2 (286)	89.8 (1,236)	71.4 (75)	86.4 (400)	FPSV≠T
Married, % (n)	56.3 (371)	52.7 (173)	57.1 (786)	61.9 (65)	57.2 (265)	No Differences
White Non-Hispanic, % (n)	63.9 (421)	66.8 (219)	60.2 (829)	62.9 (66)	73.7 (341)	FS≠V
Black Non-Hispanic, % (n)	17.5 (115)	15.9 (52)	18.8 (258)	17.1 (18)	10.2 (47)	FS≠V
Hispanic, % (n)	9.1 (60)	11.9 (39)	12.1 (166)	13.3 (14)	9.3 (43)	No Differences
OEF/OIF/OND Veteran, % (n)	71.2 (469)	72.0 (236)	68.2 (938)	75.2 (79)	66.1 (306)	No Differences
Homeless, % (n)	5.0 (33)	5.5 (18)	5.1 (70)	2.9 (3)	5.2 (24)	No Differences
Combat Exposure, % (n)	28.5 (188)	36.6 (120)	28.2 (388)	30.5 (32)	25.3 (117)	P≠SV
Sexual Trauma in Military, % (n)	12.0 (79)	13.4 (44)	11.0 (151)	24.8 (26)	13.4 (62)	FSV≠T
VA Disability Level ≥ 70, % (n)	66.3 (437)	67.4 (221)	67.0 (922)	74.3 (78)	73.4 (340)	No Differences
Service Use Characteristics						
Plurality of Care at a VAMC, % (n)	59.9 (395)	65.9 (216)	65.9 (907)	69.5 (73)	70.2 (325)	F≠V
AMT from a MH prescriber, % (n)	88.9 (586)	87.8 (288)	89.9 (1,237)	33.3 (35)	85.3 (395)	FPSV≠T
Primary Care Visits, M (SD)	3.5 (2.9)	3.6 (2.8)	3.5 (3.0)	4.9 (4.1)	4.0 (2.9)	FPS≠T, S≠V
Any Individual Therapy, % (n)	98.5 (649)	98.5 (323)	98.3 (1,353)	98.1 (103)	98.9 (458)	No Differences
Total visits, index year, M (SD)	16.1 (11.1)	15.5 (10.5)	15.8 (11.6)	16.0 (11.6)	18.1 (12.6)	FPS≠V
EBP-I, index year, M (SD)	3.4 (4.9)	3.1 (4.8)	3.6 (5.1)	3.8 (5.2)	3.2 (4.8)	No Differences
EBP-I, baseline-midpoint, M (SD)	0.9 (2.0)	0.7 (1.7)	0.8 (1.8)	1.0 (1.9)	0.7 (1.6)	No Differences
EBP-I, midpoint-end, M (SD)	1.6 (3.0)	1.4 (2.6)	1.7 (3.1)	1.8 (3.2)	1.5 (2.8)	No Differences
Any Group Therapy, % (n)	59.9 (395)	61.6 (202)	62.8 (864)	56.2 (59)	63.7 (295)	No Differences

Agent	Fluoxetine	Paroxetine	Sertraline	Topiramate	Venlafaxine	
Total Visits, Index Year, M (SD)	11.9 (24.4)	12.0 (22.2)	14.2 (26.2)	11.3 (24.4)	16.9 (33.0)	F≠V
CPT-G, index year, M (SD)	2.1 (4.5)	2.1 (4.0)	2.5 (4.7)	2.5 (4.8)	2.8 (5.1)	No Differences
CPT-G, baseline-midpoint, M (SD)	0.5 (1.9)	0.4 (1.5)	0.6 (2.0)	0.6 (3.2)	0.5 (1.9)	No Differences
CPT-G, mid-endpoint, M (SD)	1.2 (3.2)	1.2 (2.9)	1.2 (3.0)	1.1 (2.6)	1.5 (3.3)	No Differences
EBP visits before AMT, M (SD)	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)	No Differences
Other Mental Health Visits, M (SD)	14.1 (11.3)	15.3 (13.1)	15.2 (14.2)	17.0 (16.6)	17.3 (15.6)	FS≠V
Substance Abuse Visits, M (SD)	3.5 (14.4)	3.1 (14.3)	4.1 (17.7)	1.2 (5.8)	4.4 (18.4)	No Differences
Comorbid Diagnoses						
Pain Disorder, % (n)	73.1 (482)	78.0 (256)	75.0 (1,032)	84.8 (89)	79.7 (369)	No Differences
Headache Disorder, % (n)	36.9 (243)	40.2 (132)	39.0 (537)	81.9 (86)	48.8 (226)	FS≠VT, P≠T, T≠V
Psychotic Disorders, % (n)	3.6 (24)	4.0 (13)	3.3 (45)	7.6 (8)	2.6 (12)	No Differences
Bipolar Mood Disorders, % (n)	5.6 (37)	5.5 (18)	5.7 (79)	8.6 (9)	5.6 (26)	No Differences
Depressive Mood Disorders, % (n)	79.4 (523)	77.4 (254)	79.4 (1,093)	69.5 (73)	84.0 (389)	T≠V
Anxiety Disorders, % (n)	41.3 (272)	44.2 (145)	41.1 (565)	41.0 (43)	52.3 (242)	FS≠V
TBI and Cognitive Disorders, % (n)	25.6 (169)	26.5 (87)	26.2 (361)	43.8 (46)	29.4 (136)	FPSV≠T
Personality Disorders, % (n)	5.5 (36)	6.4 (21)	4.3 (59)	2.9 (3)	6.3 (29)	No Differences
Nicotine Dependence, % (n)	42.5 (280)	52.7 (173)	42.6 (586)	32.4 (34)	48.8 (226)	FST≠P, T≠V
Alcohol Dependence, % (n)	33.1 (218)	33.2 (109)	29.0 (399)	18.1 (19)	29.2 (135)	FP≠T
Marijuana Dependence, % (n)	6.2 (41)	4.9 (16)	4.1 (57)	2.9 (3)	5.2 (24)	No Differences
Opioid Dependence, % (n)	4.7 (31)	6.4 (21)	3.7 (51)	2.9 (3)	5.0 (23)	No Differences
						Concurrent Medication Use
Other Antidepressant, % (n)	68.4 (451)	69.8 (229)	69.1 (951)	79.0 (83)	70.6 (327)	No Differences
Other Anticonvulsant, % (n)	32.6 (215)	36.0 (118)	30.5 (419)	39.0 (41)	43.8 (203)	FS≠V
Lithium, % (n)	2.7 (18)	1.2 (4)	1.6 (22)	1.9 (2)	3.0 (14)	No Differences
Antipsychotic, % (n)	25.8 (170)	28.4 (93)	25.8 (355)	30.5 (32)	35.2 (163)	FS≠V
Sedative/Hypnotics, % (n)	52.8 (348)	57.0 (187)	49.0 (674)	61.0 (64)	59.4 (275)	S≠V
Opioids, % (n)	38.8 (256)	45.1 (148)	37.7 (519)	54.3 (57)	49.9 (231)	FS≠VT
Prazosin, % (n)	41.9 (276)	43.0 (141)	44.7 (615)	37.0 (35.2)	46.7 (216)	No Differences
Stimulants, % (n)	5.8 (38)	3.0 (10)	3.3 (46)	5.7 (6)	6.3 (29)	No Differences

Note. PTSD=Posttraumatic Stress Disorder, FY=Fiscal Year, PCL=PTSD Checklist, M=mean, SD=standard Deviation, OEF/OIF/OND=Operations Enduring Freedom/Iraqi Freedom/New Dawn, VA= Veterans Affairs, VAMC=VA Medical Center; AMT=Adequate Medication Trial, MH=Mental Health, EBP-I=Individual Evidence-Based Psychotherapy, CPT-G=Group Cognitive Processing Therapy, TBI=Traumatic Brain Injury

Table 3:

Participants with an Adequate Trial of an Effective Medication for PTSD plus Outcomes Measurement, 2008–2013 (Weighted)

Agent	Fluoxetine n=659	Paroxetine n=328	Sertraline n=1,376	Topiramate n=105	Venlafaxine n=463	Pairwise Differences
Baseline Symptoms and Alignment of Medication Initiation and Baseline Measurement						
Baseline PCL Score, M (SD)	61.9 (12.0)	62.1 (12.0)	62.0 (12.0)	62.6 (16.2)	62.3 (12.4)	No Differences
Baseline PCL Score before initiation, % (n)	43.4 (334)	45.0 (164)	39.8 (508)	40.2 (37)	37.3 (137)	No Differences
Baseline PCL Score during titration, % (n)	13.6 (47)	12.8 (26)	18.7 (338)	29.3 (25)	17.5 (85)	FP≠STV
Baseline PCL Score full dose, % (n)	43.0 (278)	42.2 (138)	41.5 (530)	30.5 (43)	45.2 (241)	No Differences
						Demographic Characteristics
Age, M (SD)	39.6 (13.1)	39.9 (13.3)	40.4 (12.9)	40.6 (16.0)	39.9 (12.8)	No Differences
Men, % (n)	87.9 (580)	87.0 (286)	89.1 (1,236)	83.4 (75)	88.1 (400)	No Differences
Married, % (n)	57.1 (371)	53.6 (173)	57.1 (786)	64.6 (65)	60.2 (265)	No Differences
White Non-Hispanic, % (n)	64.5 (421)	66.2 (219)	62.4 (829)	57.9 (66)	67.1 (341)	No Differences
Black Non-Hispanic, % (n)	16.6 (115)	16.5 (52)	17.4 (258)	21.6 (18)	13.9 (47)	No Differences
Hispanic, % (n)	9.4 (60)	12.3 (39)	11.6 (166)	9.2 (14)	11.4 (43)	No Differences
OEF/OIF/OND Veteran, % (n)	71.1 (469)	70.1 (236)	69.6 (938)	71.9 (79)	68.5 (306)	No Differences
Homeless, % (n)	4.8 (33)	4.4 (18)	5.1 (70)	1.8 (3)	3.8 (24)	No Differences
Combat Exposure, % (n)	28.3 (188)	31.9 (120)	27.9 (388)	23.5 (32)	27.4 (117)	No Differences
Sexual Trauma in Military, % (n)	12.5 (79)	14.2 (44)	11.3 (151)	16.3 (26)	11.5 (62)	No Differences
VA Disability Level ≥ 70, % (n)	67.6 (437)	67.4 (221)	67.6 (922)	76.6 (78)	70.8 (340)	No Differences
Service Use Characteristics						
Plurality of Care at a VAMC, % (n)	62.7 (395)	66.5 (216)	65.7 (907)	53.5 (73)	67.4 (325)	No Differences
AMT from a MH prescriber, % (n)	88.4 (586)	89.3 (288)	88.1 (1,237)	84.7 (35)	85.9 (395)	No Differences
Primary Care Visits, M (SD)	3.6 (3.2)	3.6 (2.8)	3.6 (3.2)	4.4 (5.5)	3.7 (2.8)	No Differences
Any Individual Therapy, % (n)	98.6 (649)	98.8 (323)	98.5 (1,353)	99.8 (103)	98.9 (458)	No Differences
Total visits, index year, M (SD)	16.1 (12.0)	15.6 (11.1)	15.9 (11.4)	15.0 (14.4)	16.4 (11.1)	No Differences
EBP-I, index year, M (SD)	3.3 (5.1)	3.2 (5.2)	3.5 (5.1)	3.1 (6.8)	3.2 (5.1)	No Differences
EBP-I, baseline-midpoint, M (SD)	0.8 (1.8)	0.8 (1.8)	0.8 (1.8)	0.7 (2.5)	0.7 (1.8)	No Differences
EBP-I, midpoint-end, M (SD)	1.6 (3.2)	1.4 (2.8)	1.6 (3.0)	1.6 (4.3)	1.5 (2.7)	No Differences
Any Group Therapy, % (n)	61.0 (395)	62.0 (202)	61.7 (864)	52.8 (59)	61.2 (295)	No Differences
Total Visits, Index Year, M (SD)	11.7 (23.6)	12.2 (25.1)	13.6 (25.6)	13.4 (54.3)	13.0 (22.4)	No Differences
CPT-G, index year, M (SD)	2.1 (4.5)	2.1 (4.0)	2.5 (4.7)	2.5 (4.8)	2.8 (5.1)	No Differences
CPT-G, baseline-midpoint, M (SD)	0.4 (1.9)	0.4 (2.0)	0.6 (2.4)	0.2 (1.1)	0.5 (2.1)	No Differences
CPT-G, midpoint-end, M (SD)	1.0 (3.6)	1.1 (3.7)	1.2 (4.4)	0.8 (3.3)	1.3 (3.6)	No Differences
EBP visits before AMT, M (SD)	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)	0.1 (0.5)	0.2 (0.4)	No Differences

Agent	Fluoxetine n=659	Paroxetine n=328	Sertraline n=1,376	Topiramate n=105	Venlafaxine n=463	Pairwise Differences
Other Mental Health Visits, M (SD)	14.4 (12.4)	14.6 (11.2)	15.3 (14.8)	17.6 (24.4)	15.1 (11.9)	No Differences
Substance Abuse Visits, M (SD)	2.9 (11.4)	2.8 (12.7)	3.7 (15.4)	1.9 (8.7)	3.4 (14.1)	No Differences
Comorbid Diagnoses						
Pain Disorder, % (n)	74.5 (482)	78.0 (256)	75.8 (1,032)	77.4 (89)	76.9 (369)	No Differences
Headache Disorder, % (n)	40.0 (243)	40.1 (132)	40.6 (537)	56.0 (86)	43.3 (226)	No Differences
Psychotic Disorders, % (n)	3.7 (24)	3.1 (13)	3.4 (45)	5.5 (8)	2.3 (12)	No Differences
Bipolar Mood Disorders, % (n)	5.8 (37)	5.0 (18)	6.2 (79)	13.0 (9)	4.6 (26)	No Differences
Depressive Mood Disorders, % (n)	78.5 (523)	78.3 (254)	79.7 (1,093)	76.7 (73)	81.3 (389)	No Differences
Anxiety Disorders, % (n)	41.3 (272)	44.4 (145)	42.1 (565)	41.9 (43)	45.7 (242)	No Differences
TBI and Cognitive Disorders, % (n)	26.6 (169)	25.4 (87)	27.4 (361)	43.7 (46)	27.1 (136)	No Differences
Personality Disorders, % (n)	5.4 (36)	5.7 (21)	4.6 (59)	2.4 (3)	4.8 (29)	No Differences
Nicotine Dependence, % (n)	42.4 (280)	47.1 (173)	43.7 (586)	30.9 (34)	46.1 (226)	No Differences
Alcohol Dependence, % (n)	31.7 (218)	32.6(109)	29.1 (399)	23.7 (19)	27.4 (135)	No Differences
Marijuana Dependence, % (n)	5.0 (41)	4.2 (16)	4.0 (57)	2.7 (3)	3.9 (24)	No Differences
Opioid Dependence, % (n)	4.7 (31)	5.7 (21)	3.9 (51)	3.5 (3)	3.4 (23)	No Differences
						Concurrent Medication Use
Other Antidepressant, % (n)	68.6 (451)	68.7 (229)	69.3 (951)	70.6 (83)	69.0 (327)	No Differences
Other Anticonvulsant, % (n)	34.0 (215)	35.5 (118)	32.4 (419)	35.9 (41)	36.3 (203)	No Differences
Lithium, % (n)	2.4 (18)	0.7 (4)	1.7 (22)	4.3 (2)	2.3 (14)	No Differences
Antipsychotic, % (n)	26.5 (170)	25.8 (93)	26.3 (355)	32.1 (32)	30.1 (163)	No Differences
Sedative/Hypnotics, % (n)	53.1 (348)	55.6 (187)	51.1 (674)	53.8 (64)	54.8 (275)	No Differences
Opioids, % (n)	39.5 (256)	45.1 (148)	39.8 (519)	50.8 (57)	42.5 (231)	No Differences
Prazosin, % (n)	41.3 (276)	40.9 (141)	44.8 (615)	31.2 (37)	44.9 (216)	No Differences
Stimulants, % (n)	4.6 (38)	2.5 (10)	3.6 (46)	2.4 (6)	5.2 (29)	No Differences

Note. PTSD=Posttraumatic Stress Disorder, PCL=PTSD Checklist, M=mean, SD=standard Deviation, OEF/OIF/OND=Operations Enduring Freedom/Iraqi Freedom/New Dawn, VA= Veterans Affairs, VAMC=VA Medical Center; AMT=Adequate Medication Trial, MH=Mental Health, EBP-I=Individual Evidence-Based Psychotherapy, CPT-G=Group Cognitive Processing Therapy, TBI=Traumatic Brain Injury

Table 4:

Outcomes for Participants with an Adequate Trial of an Effective Medication for PTSD plus Outcomes Measurement (Unweighted)

Agent	Fluoxetine n=659	Paroxetine n=328	Sertraline n=1,376	Topiramate n=105	Venlafaxine n=463	Pairwise Differences
Raw Outcomes						
Baseline PCL Score, M (SD)	61.8 (11.8)	62.2 (12.1)	62.0 (11.7)	61.5 (12.6)	62.5 (12.0)	No Differences
Change in PCL, M (SD)	-6.2 (14.0)	-6.2 (15.1)	-6.1 (14.1)	-6.3 (13.8)	-5.0 (13.3)	No Differences
5-Point Drop in PCL, % (n)	51.9 (342)	50.9 (167)	50.1 (689)	42.9 (45)	47.9 (222)	No Differences
10-Pt. Drop plus Loss of Diagnosis, % (n)	17.6 (116)	20.4 (67)	17.2 (237)	16.2 (17)	13.6 (63)	No Differences
						Symptom Clusters
Baseline Reexperiencing, M (SD)	17.7 (4.3)	17.8 (4.2)	17.8 (4.1)	17.9 (4.4)	17.9 (4.2)	No Differences
Change in Reexperiencing, M (SD)	-1.7 (4.8)	-1.8 (4.8)	-1.6 (4.6)	-2.0 (5.1)	-1.2 (4.6)	No Differences
Baseline Avoidance, M (SD)	7.6 (1.9)	7.8 (1.8)	7.7 (1.9)	7.4 (2.0)	7.6 (2.0)	No Differences
Change in Avoidance, M (SD)	-0.7 (2.4)	-0.9 (2.5)	-0.8 (2.4)	-0.6 (2.3)	-0.6 (2.3)	No Differences
Baseline Numbing, M (SD)	17.3 (4.3)	17.0 (4.3)	17.2 (4.3)	16.9 (4.6)	17.5 (4.3)	No Differences
Change in Numbing, M (SD)	-1.8 (4.8)	-1.5 (5.2)	-1.8 (5.0)	-1.7 (4.9)	-1.5 (4.8)	No Differences
Baseline Hyperarousal, M (SD)	19.4 (3.9)	19.5 (4.0)	19.4 (3.8)	19.5 (4.1)	19.6 (3.8)	No Differences
Change in Hyperarousal, M (SD)	-2.0 (4.6)	-1.8 (4.8)	-1.9 (4.5)	-2.1 (4.5)	-1.8 (4.3)	No Differences
Baseline Sleep, M (SD)	7.4 (1.9)	7.6 (1.9)	7.5 (1.9)	7.4 (2.1)	7.6 (1.9)	No Differences
Change in Sleep, M (SD)	-0.8 (2.2)	-0.9 (2.1)	-0.8 (2.1)	-0.8 (2.4)	-0.6 (2.1)	No Differences

Note. PTSD=Posttraumatic Stress Disorder, PCL=PTSD Checklist, M=mean, SD=standard deviation

Table 5:

Outcomes for Participants with an Adequate Trial of an Effective Medication for PTSD plus Outcomes Measurement (Weighted)

Agent	Fluoxetine n=659	Paroxetine n=328	Sertraline n=1,376	Topiramate n=105	Venlafaxine n=463	Pairwise Differences
Raw Outcomes						
Baseline PCL, M (SD)	61.9 (12.1)	62.0 (12.1)	62.0 (11.9)	62.7 (16.0)	62.3 (12.3)	No Differences
Change in PCL, M (SD)	-5.8 (14.4)	-5.6 (15.4)	-6.0 (14.6)	-5.0 (22.1)	-5.1 (14.4)	No Differences
5-Point Drop in PCL, % (n)	51.1 (342)	50.2 (167)	49.7 (689)	40.4 (45)	48.3 (222)	No Differences
10-Pt. Drop plus Loss of Diagnosis, % (n)	17.3 (116)	19.3 (67)	17.3 (237)	15.5 (17)	14.2 (63)	No Differences
						Symptom Clusters
Baseline Reexperiencing, M (SD)	17.7 (4.4)	17.8 (4.2)	17.8 (4.2)	17.5 (7.0)	17.8 (4.4)	No Differences
Change in Reexperiencing, M (SD)	-1.6 (4.9)	-1.6 (5.1)	-1.6 (4.9)	-1.0 (8.6)	-1.2 (5.0)	No Differences
Baseline Avoidance, M (SD)	7.6 (2.0)	7.7 (1.9)	7.6 (2.0)	7.6 (2.7)	7.5 (2.1)	No Differences
Change in Avoidance, M (SD)	-0.7 (2.5)	-0.8 (2.7)	-0.8 (2.6)	-0.6 (3.6)	-0.6 (2.4)	No Differences
Baseline Numbing, M (SD)	17.2 (4.4)	17.0 (4.3)	17.2 (4.5)	18.0 (5.2)	17.4 (4.5)	No Differences
Change in Numbing, M (SD)	-1.6 (5.0)	-1.3 (5.3)	-1.7 (5.2)	-2.0 (8.2)	-1.5 (5.3)	No Differences
Baseline Hyperarousal, M (SD)	19.4 (4.1)	19.4 (4.2)	19.4 (3.8)	19.7 (5.8)	19.6 (4.1)	No Differences
Change in Hyperarousal, M (SD)	-1.8 (4.8)	-1.7 (4.8)	-1.9 (4.7)	-1.7 (7.3)	-1.9 (4.9)	No Differences
Baseline Sleep, M (SD)	7.4 (2.0)	7.6 (1.9)	7.5 (1.9)	7.3 (3.3)	7.5 (2.1)	No Differences
Change in Sleep, M (SD)	-0.7 (2.3)	-0.7 (2.2)	-0.7 (2.3)	-0.4 (3.8)	-0.6 (2.5)	No Differences

Note. PTSD=Posttraumatic Stress Disorder, PCL=PTSD Checklist, M=mean, SD=standard deviation

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ORIGINAL PAPER

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Using patient-reported outcomes to understand the effectiveness of guideline-concordant care for post-traumatic stress disorder in clinical practice

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Abstract

Rationale: Identifying predictors of improvement amongst patients receiving routine treatment for post-traumatic stress disorder (PTSD) could provide information about factors that influence the clinical effectiveness of guideline-concordant care. This study builds on prior work by accounting for delivery of specific evidence-based treatments (EBTs) for PTSD while identifying potential predictors of clinical improvement using patient-reported outcomes measurement.

Method: Our sample consisted of 2 643 US Department of Veterans Affairs (VA) outpatients who initiated treatment for PTSD between 2008 and 2013 and received at least four PTSD checklist (PCL) measurements over 12 weeks. We obtained PCL data as well as demographic, diagnostic, and health services use information from the VA corporate data warehouse. We used latent trajectory analysis to identify classes of patients based on PCL scores, then determined demographic, diagnostic, and treatment predictors of membership in each class.

Results: Patients who met our PCL-based inclusion criteria were far more likely than those who did not receive EBTs. We identified two latent trajectories of PTSD symptoms. Patients in the substantial improvement group (25.9%) had a mean decrease in PCL score of 16.24, whereas patients in the modest improvement group improved by a mean of 8.09 points. However, there were few differences between the groups, and our model to predict group membership was only slightly better than chance (area under the curve [AUC] = 0.55). Of the 64 covariates we tested, the only robust individual predictor of improvement was gender, with men having lower odds of being in the substantial improvement group compared with women (odds ratio [OR] 0.76; 95% confidence interval [CI] 0.58-0.96).

Conclusion: VA patients with PTSD can realize significant improvement in routine clinical practice. Although available medical records-based variables were generally insufficient to predict improvement trajectory, this study did indicate that men have lower odds of substantial improvement than women.

KEYWORDS

delivery of health care, evidence-based medicine, mental health services, patient reported outcome measures, post-traumatic stress disorder, practice guideline

1 | INTRODUCTION

Post-traumatic stress disorder (PTSD) is a serious condition that can follow exposure to a traumatic event, characterized by intrusive re-experiencing of the trauma such as flashbacks and nightmares, avoidance of trauma reminders that are associated with or arouse intrusive symptoms, negative alterations in cognitions and mood such as inability to remember the trauma or inability to experience positive emotions, and increased arousal and reactivity such as exaggerated startle response and angry outbursts.[1] PTSD has a lifetime prevalence of 6.1% in the United States.[2] Over 10% of veterans receiving care in the Department of Veterans Affairs (VA) health-care system have PTSD, comprising an active caseload of approximately 600 000 in 2016.[3] VA patients often receive PTSD treatment for many years,[4] despite randomized controlled trials indicating that evidence-based treatments (EBTs) for PTSD are generally delivered over a 2 to 4 month time frame.[5]

To monitor progress towards recovery, VA clinicians increasingly rely on patient-reported outcome measurement using the PTSD Checklist (PCL)[6] as part of routine practice.[7] Leveraging patient-reported outcome measurement, such as longitudinal PCL data, to understand and improve the course of routine clinical treatment at the population level has been suggested as a method to expand the available evidence base in a learning health-care system.[8-10] Such work might allow health systems to learn about the factors that predict that patients do not benefit sufficiently from routine clinical care and to take steps to improve systems to improve health-care effectiveness for those patients. Consistent with this idea, Sripada et al (2017) recently performed the first national study using latent class analysis of VA PCL data to demonstrate typical symptomatic trajectories in clinical practice.[11] They identified VA patients with new PTSD diagnoses nationally in 2013, including 2237 who had four PCL scores evenly spaced over a 12-week period. They found three classes of patients including mild-improving (21.8%), moderate-improving (43.8%), and severe-stable (34.3%). Predictors of mild or moderate improvement, compared with the severe-stable class, were female gender, White race, non-Hispanic ethnicity, and a lack of comorbid depression. However, there were two important limitations to this work. First, the authors did not apply PTSD diagnostic criteria to the baseline PCL score when defining their cohort. As such, it is possible that some patients did not have PTSD at the start of their trajectory period. Second, the authors did not account for receipt of EBTs, including medications and psychotherapy in their models predicting class membership. Thus, it was not possible to determine whether membership in improving groups was driven by receipt of guideline-concordant care.

Consistent with the results of the plurality of meta-analyses,[5,12-15] the VA/Department of Defense (DoD) clinical practice guideline (CPG) recommends four antidepressants for PTSD, including fluoxetine, sertraline, paroxetine, and venlafaxine.[16] The CPG recommends many trauma-focused psychotherapy protocols for PTSD, including prolonged exposure (PE), cognitive processing therapy (CPT), eye movement desensitization and reprocessing (EMDR), other specific cognitive behavioural therapies, brief eclectic psychotherapy, narrative exposure therapy, and written narrative exposure.[16] Below, we refer to the four medications as evidence-based antidepressants (EBAs) and the trauma-focused psychotherapies as evidence-based psychotherapies (EBPs). For most of the past decade, VA training efforts have focused on two EBPs, PE and CPT.[17]

We sought to extend the work of Sripada et al by including variables describing EBT provision as additional predictors of clinical trajectory group membership using a national sample of VA patients undergoing new episodes of PTSD care. Our goal was to identify predictors of clinical improvement while accounting for the delivery of EBTs. We hoped that contextualizing patient predictors of improvement with data about EBT receipt could provide information about which VA PTSD treatments work the best and for whom in routine clinical practice. Individual patient factors that continue to predict lack of improvement after accounting for EBT receipt would more strongly indicate that disparities in effectiveness are determined by those patient factors rather than differences in access to EBT.

2 | METHOD

2.1 | Patients and procedure

The sample was drawn from a cohort of VA patients with new PTSD treatment episodes from fiscal years 2004 through 2013, which was designed to examine patterns of care during the initial year of treatment.[18-20] We used the VA corporate data warehouse (CDW) to obtain information on services use, clinical diagnoses, prescriptions, and standardized measures of PTSD symptoms. This study was approved by the Veterans Institutional Review Board of Northern New England.

The cohort included patients who received a primary diagnosis of PTSD at two or more outpatient encounters, at least one of which occurred in a mental health setting, over the course of 90 days between fiscal years 2004 and 2013. This criterion is consistent with research that indicates requiring multiple encounter-based diagnoses, including those made by a mental health clinician, improves the validity of encounter-based diagnoses for PTSD case identification.[21-23] To focus on new episodes of PTSD care, patients who had met this criterion during the prior 2 years were excluded, requiring us to look back into fiscal years 2002 and 2003 records. For example, if a patient met our inclusion criteria on June 30, 2002, he or she would not have been eligible for cohort inclusion until July 1, 2004. Additionally, when patients met our criteria for cohort inclusion multiple times over the 10-year period, only the first episode was included. For example, a patient who entered the cohort in fiscal year 2004 and did not receive any PTSD diagnoses in fiscal years 2008 or 2009 could not have re-entered the fiscal year 2010 or later. Because of a lack of data from patient-reported outcome measurement using the PCL during the years 2004 to 2007, the sample was further restricted to those who entered the cohort in fiscal year 2008 or later, when use of the PCL began to increase.[24,25] We examined 1 year of treatment receipt following the first encounter with a qualifying diagnosis of PTSD (index diagnosis). Patients were included in our analytic sample if they met our criteria for PTSD symptoms measurement (described below) at some point during the year following their index diagnosis.

2.2 | Measures

We measured PTSD symptoms using the PCL. During the time period we examined, the VA used the version of the PCL corresponding to PTSD diagnostic criteria in the fourth version of the Diagnostic and Statistical Manual of Mental Disorders, called DSM-IV.[26,27] The PCL is a 17-item measure with each item rated on a five-point Likert-type scale with total scores ranging from 17 through 85.[6] Respondents are asked to rate how much they are bothered by each symptom over the last month. Symptom presence is determined by a response of "moderately" or greater.[6] We defined clinically meaningful improvement as a decrease of 10 points or more based on prior research in Veterans showing that 5 to 10 points is clinically meaningful.[28,29] A clinically meaningful improvement in PTSD symptoms plus no longer meeting diagnostic criteria for PTSD has been shown to be an important marker of improved quality of life.[30]

Consistent with the approach of Sripada et al to cohort inclusion, we required a minimum of four PCL scores over the course of 12 weeks, and that the timing of these PCL scores was spread across at least four of six 2-week windows (Weeks 1-2, 3-4, 5-6, 7-8, 9-10, and 11-12).[31] To ensure patients continued to experience PTSD at the start of their trajectory period, we differed from Sripada et al in requiring that patients have a score of 50 or higher,[6,32] and meet minimal symptom criteria according to DSM-IV (one re-experiencing symptom, three avoidance and numbing symptoms, and two hyperarousal symptoms) at their baseline PCL measurement.

2.3 | Independent variables

We used an extensive list of medical records-based covariates that could plausibly be associated with our outcome of PTSD symptom change.[7] Patient characteristics included demographics, military service characteristics, and commonly occurring medical and mental health disorders. We measured health-care utilization variables for all patients during their initial year of PTSD treatment. Outpatient visits included those to primary care, general mental health, specialized PTSD, and substance abuse specialty clinics. We also measured days of care in residential PTSD or substance abuse settings or in the acute inpatient psychiatry setting. EBA receipt included any filled prescription for fluoxetine, sertraline, paroxetine, or venlafaxine as well as weeks filled of each. We measured EBP receipt, including sessions of PE and CPT, using natural language processing (NLP) algorithms to classify therapists' notes.[4] During initial development of the NLP classifiers, we attempted to identify other EBPs for PTSD such as EMDR.[33] Despite manual review of over 7500 notes written about patients attending PTSD clinics, we were unable to detect any examples of other EBPs in routine clinical practice in VA.[33] Therefore, our EBP for PTSD measure only included PE and CPT sessions. We further distinguished CPT sessions as being delivered in individual (CPT-I) or group (CPT-G) settings based on procedural billing codes. Our NLP algorithms have an overall classification accuracy of 0.99 for PE, 0.97 for CPT-I, and 0.97 for CPT-G.[4] Other mental health treatment variables included non-EBP psychotherapy provision as well as provision of non-EBA medications commonly prescribed to patients in this cohort.[34]

2.4 | Data analysis

To understand how patients selected for this analysis differed from the rest of the cohort during the relevant years, we compared patient characteristics and service use over the initial year of PTSD treatment using χ^2 analysis and t tests, as appropriate. We similarly compared these same characteristics based on group assignment during the 12-week trajectory period amongst patients who met our PCL-based inclusion criteria. We identified improvement groups with latent trajectory analysis using the R traj package to implement the Leffondre et al (2004) method.[35] This method was developed to identify patterns of change in large clinical databases containing repeated measures, where measurement intervals may be irregular. It has been applied broadly to detect and understand patterns of illness in general medical and mental health conditions.[36-38] In this application, we used patients' PCL scores to calculate 24 potential measures of change over time.[39] Several of the measures of change are meaningful only if there are at least four observations per patient, necessitating the requirement of at least four PCL scores for cohort inclusion.[35] After calculation of the measures, we performed factor analysis to select the subset of nonredundant measures, and cluster analysis to identify subgroups of patients with similar PTSD symptom trajectories. We determined the number of clusters based on examination of cubic clustering criterion and scree plots.

TABLE 1 Characteristics of all VA patients with new episodes of PTSD care from 2008 to 2013 and final sample

	Overall (n = 491 040)		Final Sample (0.5%; n = 2,643)		
	M or %	SD or n	M or %	SD or n	*P*
Demographic characteristics at time of initial PTSD diagnosis					
Age, M, SD	48.55	16.00	47.09	14.74	<.001
Men, %, n	90.7	445 583	83.1	2195	<.001
Married, %, n	52.7	258 764	53.8	1422	.254
White non-Hispanic, %, n	63.5	311 756	60.3	1594	<.001
Black non-Hispanic, %, n	19.1	93 666	21.6	571	<.001
Hispanic, %, n	8.1	39 827	8.7	229	.296
OEF/OIF/OND veteran, %, n	34.9	171 364	38.4	1014	<.001
Rural, %, n	35.0	171 644	31.9	842	<.001
Homeless, %, n	5.4	26 574	7.5	199	<.001
Combat exposure, %, n	28.6	140 344	23.8	630	<.001
Sexual trauma while in military, %, n	9.3	45 803	17.2	455	<.001
VA disability level 70 or greater, %, n	55.7	273 242	55.6	1470	.978
Comorbid diagnoses in the year following initial PTSD diagnosis					
Pain disorder, %, n	64.9	318 802	68.8	1818	<.001
Headache disorder, %, n	25.1	123 441	31.9	842	<.001
Psychotic disorders, %, n	4.2	20 682	2.7	71	<.001
Bipolar mood disorders, %, n	6.2	30 560	5.4	143	.083
Depressive mood disorders, %, n	60.3	296 071	73.5	1943	<.001
Non-PTSD anxiety disorders, %, n	28.5	139 779	37.8	1000	<.001
TBI and cognitive disorders, %, n	13.4	65 834	14.8	391	.036
Personality disorders, %, n	3.9	18 959	4.2	110	.421
Nicotine dependence, %, n	39.0	191 712	33.7	891	<.001
Alcohol dependence, %, n	22.6	111 027	24.6	650	.015
Marijuana dependence, %, n	3.2	15 586	3.4	89	.570
Opioid dependence, %, n	3.2	15 903	3.5	92	.481
Service utilization during year following index PTSD diagnosis					
Any OP primary care visits, %, n	92.3	453 051	93.3	2466	.045
OP primary care visits, M, SD	5.52	5.63	6.12	5.24	<.001
Any OP general MH visits, %, n	99.9	490 511	99.9	2640	.928
OP general MH visits, M, SD	18.24	22.53	35.84	26.93	<.001
Any OP specialized PTSD visits, %, n	44.6	218 827	75.1	1986	<.001
OP specialized PTSD visits, M, SD	10.48	11.90	20.05	13.92	<.001
Any OP SA visits, %, n	14.6	71 513	18.9	500	<.001
OP SA visits, M, SD	18.88	28.59	22.80	26.11	.002
Any residential PTSD treatment, %, n	2.1	10 375	6.6	173	<.001
Days of residential PTSD, M, SD	60.49	56.15	65.47	46.15	.240
Any residential SA treatment, %, n	2.6	12 723	3.6	96	<.001
Days of residential SA, M, SD	69.74	69.72	88.90	77.56	.007
Any inpatient MH treatment, % (n)	7.0	34 386	8.0	210	.057
Days of inpatient MH, M, SD	20.58	39.49	21.27	35.00	.799
Evidence-based treatment for PTSD receipt during first year following index diagnosis					
Any PE, %, n	2.8	13 673	26.6	702	<.001

(Continues)

TABLE 1 (Continued)

	Overall (n = 491 040)		Final Sample (0.5%; n = 2,643)		
	M or %	SD or n	M or %	SD or n	*P*
Sessions of PE, M, SD	5.51	4.41	7.42	4.61	<.001
Any individual CPT, %, n	6.6	32 311	54.4	1,438	<.001
Sessions of individual CPT, M, SD	5.44	4.70	8.12	4.99	<.001
Any group CPT, %, n	3.5	17 330	26.1	691	<.001
Sessions of CPT, M, SD	6.37	5.29	8.52	4.91	<.001
Any fluoxetine, %, n	10.7	52 405	11.4	302	.208
Weeks supply of fluoxetine, M, SD	27.02	18.62	26.69	18.33	.755
Any paroxetine, %, n	5.8	28 628	6.7	176	.068
Weeks supply of paroxetine, M, SD	25.42	18.87	26.00	18.92	.691
Any sertraline, %, n	25.2	123 735	30.2	798	<.001
Weeks supply of sertraline, M, SD	26.5	18.5	29.2	18.7	<.001
Any venlafaxine, %, n	9.4	46 344	11.2	296	.002
Weeks supply of venlafaxine, M, SD	26.61	20.23	28.08	20.03	.209
Other mental health treatment receipt during year following index diagnosis					
Any non-PE/CPT individual therapy, %, n	86.1	422 545	95.7	2529	<.001
Any non-PE/CPT Group therapy, %, n	31.0	151 973	50.3	1330	<.001
Any non-F/S/P/V antidepressant, %, n	63.3	310 709	62.7	1656	.508
Any anticonvulsant, %, n	26.4	129.678	28.8	762	.005
Any sedative/hypnotics, %, n	39.7	194 690	35.2	930	<.001
Any opioid, %, n	37.2	182 514	35.0	926	.023
Any atypical antipsychotic, %, n	20.3	99 698	16.1	425	<.001
Any prazosin, %, n	18.6	91 551	26.8	708	<.001
Any nicotine replacement, %, n	11.2	54 777	11.9	315	.212
Any naltrexone or Acamprosate, %, n	1.2	5892	1.7	44	.028
Any opioid replacement therapy, %, n	0.7	3408	0.9	24	.184

Abbreviations: CPT, cognitive processing therapy; F/S/P/V, Fluoxetine/Sertraline/Paroxetine/Venlafaxine; M, mean; MH, mental health; OEF/OIF/OND, Operations Enduring Freedom/Iraqi Freedom/New Dawn; OP, outpatient; PE, prolonged exposure; PTSD, post-traumatic stress disorder; SA, substance abuse; SD, standard deviation; TBI, traumatic brain injury; VA, Department of Veterans Affairs.

After identifying symptomatic trajectories, we performed least absolute shrinkage and selection operator (LASSO) regression to predict group membership using the R glmnet package.[40] As we had many potentially redundant covariates (variables included in Table 1 as well as baseline PCL), we selected LASSO regression because it performs feature selection. LASSO is a machine learning method that avoids the overfitting common to multivariable models and the prediction errors common to stepwise selection by setting the sum of the absolute values of the regression coefficients to be less than a fixed value. This forces the coefficient of less important features to zero, and those covariates are dropped from the model. The exact penalty parameter is selected via 10-fold cross-validation. For our application, we randomly divided data into training set (2/3 of sample) and testing test (1/3 of sample). We used a 2-step process to implement LASSO regression. First, we applied LASSO on the training set to select features and passed the coefficients to the testing set to estimate the prediction score. To evaluate the association between prediction score and clustering outcome, we plotted a receiver operating characteristic (ROC) curve and estimated the area under the curve (AUC). Second, we evaluated the robustness of our feature selection using 100 bootstrapped samples in the training set. At the extreme ends of the distribution of bootstrapped replications, some features that are important in the full model are dropped by LASSO. This results in coefficients of zero. As the exponential function of zero is one, this results in an odds ratio (OR) of 1.00 for non-significant values.

3 | RESULTS

There were 491 040 patients who met our criteria for a new episode of PTSD care between fiscal years 2008 and 2013. Amongst these, only 0.5% (2643) met our inclusion criteria based on PCL data availability and baseline symptoms. The 2643 patients included in our analyses differed from the rest of the cohort in most covariates (Table 1).

With regard to demographic characteristics, they were younger, more likely to be Black (vs White), homeless, women (vs men), and to have experienced sexual trauma while in the military. They were less likely to live in a rural area, or to have been exposed to combat. Patients in the analytic cohort had similarly high levels of comorbidity to the overall treatment population, but were more likely to have pain disorders, headache disorders, depressive disorders, and non-PTSD anxiety disorders. They were less likely to have psychotic disorders or nicotine dependence. Over the year following their index PTSD diagnosis, patients in the analytic cohort had many more psychotherapy visits, including visits where they received EBPs. For example, amongst patients who met our PCL-based inclusion criteria, 26.6% received prolonged exposure and 54.4% received cognitive processing therapy in their initial year of PTSD treatment. These rates are significantly higher than in the rest of the cohort, where 2.8% received PE and 6.6% received CPT. Receipt of EBA was similar, although patients in the analytic cohort were more likely to receive sertraline and venlafaxine.

Our latent trajectory analysis indicated a 2-cluster solution (Figure 1 and Figure A1). While there was no difference in days to initial PCL (54-55 days) and baseline PCL score (severity of 65-66), the 25.9% (n = 684) of patients in the substantial improvement trajectory had a mean decrease in PCL score of 16.24 (SD = 15.42) points over 12 weeks, whereas the 74.1% (n = 1959) of patients in the modest improvement trajectory improved by a mean of 8.09 (SD = 14.40) points ($P < .001$). Similarly, 39.0% (n = 267) of patients in the substantial improvement trajectory achieved loss of PTSD diagnosis plus a 10-point improvement whereas only 16.8% (n = 329) in the modest improvement group achieved this level of improvement ($P < .001$). There were very few differences in the demographic and diagnostic characteristics or 12-week treatment receipt amongst the patients in each group (Table 2). Patients in the substantial improvement trajectory were more likely to be women, to have experienced sexual trauma while in the military, and to have comorbidities including psychotic, bipolar, personality, and alcohol use disorders. They received more outpatient mental health visits and inpatient mental health treatment. Patients in the two groups received an equal amount of EBP with the exception of group CPT, which was delivered more to patients in the modest improvement group. EBA receipt was also the same across the two groups, although patients in the substantial improvement group were slightly more likely to receive sertraline.

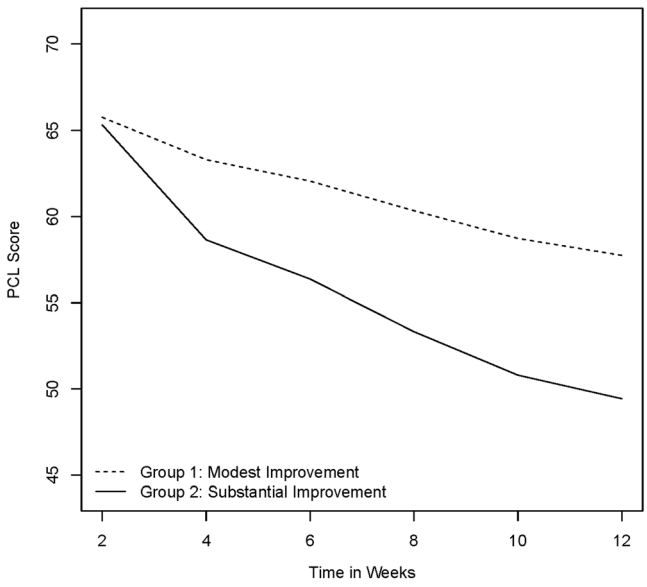

FIGURE 1 Post-traumatic stress disorder (PTSD) symptoms scores based on the PTSD checklist (PCL) over time

In the first step of our LASSO regression (model development), the ability of our model to predict group membership peaked with seven classifiers and an AUC of 0.55 (Figure 2 and Figure A2). In the second step of our LASSO regression (bootstrapping), we found that of the seven classifiers in the initial model, only gender was robust to sample selection, with an odds ratio of 0.76 men being in the substantial improvement group (95% confidence interval [CI]: 0.58-0.96). The other six classifiers were dropped by our LASSO regression model in the extreme high or low estimates, resulting in coefficients of zero and thus ORs of 1.00 (Table 3).

4 | DISCUSSION

Our results differed from those of Sripada et al[11] in that we found two rather than three PTSD symptom trajectories that both groups improved and that only the female gender predicted the level of improvement. Distinctions in our research strategies likely accounts for difference in each of these three findings. First, the difference in number of trajectories may be due to our stricter inclusion criteria for PTSD at the baseline PCL. The groups of Sripada et al had mild (mean PCL of approximately 50), moderate (approximately 60), and severe (approximately 70) PTSD symptoms at baseline. Our strategy eliminated the mild group, and our remaining groups split the difference between moderate and severe groups of Sripada et al at baseline. Second, our finding that patients in both groups improved may be related to the method used to construct our cohort. Our parent cohort was comprised of 10 yearly cross-sections of patients entering PTSD treatment between 2004 and 2013. Patients who were part of prior years' cohorts were excluded from subsequent years. Thus, in the analytic sample for this study, which included cross-sections entering PTSD treatment between 2008 and 2013, patients were either naïve to VA PTSD treatment or had not received VA PTSD treatment for many years. This is in contrast to the "180-day dormant period without a diagnosis of PTSD" of Sripada et al. Therefore, Sripada et al likely included treatment-resistant patients that would have been excluded from our sample. Finally, out of the seven predictors in our model to predict symptom trajectory, only gender was available as a covariate in the dataset of Sripada et al. Given that we used a more expanded set of patient and treatment covariates, it is not surprising that we initially found a different set of classifiers. However, in our bootstrapped analysis, only gender remained a significant predictor of symptomatic trajectory. Therefore, we are only confident in gender finding, as the other predictors may be artefacts of sampling error.

It is promising that patients in both groups experienced improvement. Even the modest improvement group was within the 5 to 10

TABLE 2 Symptomatic, demographic, diagnostic, and 12-week treatment characteristics by trajectory membership (n = 2645)

	Modest Improvement (74.1%; n = 1959)		Substantial Improvement (25.9%; n = 684)		
PTSD symptoms	**M or %**	**SD or n**	**M or %**	**SD or n**	***P***
Days from index diagnosis to PCL, M, SD	55.23	67.93	54.15	68.72	.721
Initial PCL score, M, SD	65.69	8.29	65.37	8.44	.397
Final PCL score, M, SD	57.60	14.40	49.13	15.42	<.001
Loss of PTSD diagnosis, %, n	16.8	329	39.0	267	<.001
Demographic, diagnostic, and 12-week treatment characteristics					
Age, M, SD	47.39	14.80	46.26	14.54	.085
Men, %, n	84.4	1,653	79.2	542	.002
Married, %, n	54.7	1,072	51.2	350	.109
White non-Hispanic, %, n	60.0	1,176	61.1	418	.619
Black non-Hispanic, %, n	21.6	424	21.5	147	.934
Hispanic, %, n	8.5	166	9.2	63	.555
OEF/OIF/OND, %, n	37.9	743	39.6	271	.433
Rural, %, n	31.3	614	33.3	228	.336
Homeless, %, n	7.7	150	7.2	49	.674
Combat exposure, %, n	24.3	476	22.5	154	.346
Sexual trauma while in military, %, n	16.1	315	20.5	140	.009
VA disability level 70 or greater, %, n	56.2	1101	54.0	369	.307
Pain disorder, %, n	69.1	1354	67.8	464	.534
Headache disorder, %, n	32.7	640	29.5	202	.130
Psychotic disorders, %, n	2.1	42	4.2	29	.004
Bipolar mood disorders, %, n	4.8	93	7.3	50	.011
Depressive mood disorders, %, n	73.3	1436	74.1	507	.676
Non-PTSD anxiety disorders, %, n	37.8	740	38.0	260	.912
TBI and cognitive disorders, %, n	15.4	301	13.2	90	.162
Personality disorders, %, n	3.7	72	5.6	38	.034
Nicotine dependence, %, n	33.6	659	33.9	232	.895
Alcohol dependence, %, n	23.3	456	28.4	194	.008
Marijuana dependence, %, n	3.4	66	3.4	23	.008
Opioid dependence, %, n	3.3	64	4.1	28	.310
Any primary care visits, %, n	64.1	1,255	64.5	441	.847
Primary care visits, M, SD	2.32	1.85	2.42	1.89	.318
Any OP general MH visits, %, n	99.7	1,953	99.6	681	.609
OP general MH visits, M, SD	14.50	9.24	15.48	10.21	.021
Any PTSD specialized PTSD visits, %, n	68.9	1349	66.5	455	.257
OP specialized PTSD visits, M, SD	10.87	7.08	10.97	7.52	.788
Any outpatient SA visits, M, SD	13.4	262	16.4	112	.053
Outpatient SA visits, M, SD	10.45	11.20	10.46	12.32	.997
Any residential PTSD treatment, %, n	5.1	99	6.7	46	.098
Days of residential PTSD, M, SD	51.34	16.36	52.30	18.11	.751
Any residential SA treatment, %, n	2.1	42	3.4	23	.077
Days of residential SA, M, SD	51.40	28.74	56.65	24.84	.464
Any inpatient MH treatment, %, n	1.7	33	3.4	23	.009
Days of inpatient MH treatment, M, SD	16.64	19.34	19.65	26.54	.625

(Continues)

TABLE 2 (Continued)

	Modest Improvement (74.1%; n = 1959)		Substantial Improvement (25.9%; n = 684)		
PTSD symptoms	**M or %**	**SD or n**	**M or %**	**SD or n**	***P***
Any PE, %, n	23.1	452	22.7	155	.825
Sessions of PE, M, SD	5.75	3.00	5.37	2.98	.172
Any individual CPT, %, n	49.9	977	46.2	316	.098
Sessions of individual CPT, M, SD	5.75	3.28	5.87	3.32	.564
Any group CPT, %, n	22.7	444	18.3	125	.016
Sessions of group CPT, M, SD	7.30	3.93	7.10	3.95	.609
Any fluoxetine, %, n	7.9	154	8.3	57	.695
Weeks supply of fluoxetine, M, SD	9.42	4.50	9.22	4.89	.784
Any paroxetine, %, n	5.0	98	4.8	33	.854
Weeks supply of paroxetine, M, SD	8.76	4.97	9.80	4.78	.299
Any sertraline, %, n	22.7	445	23.3	159	.776
Weeks supply of sertraline, M, SD	9.21	4.88	10.37	4.92	.011
Any venlafaxine, %, n	7.2	140	8.2	56	.371
Weeks supply of venlafaxine, M, SD	10.35	5.14	10.48	6.10	.880
Any non-PE/CPT individual therapy, %, n	81.7	1601	84.7	579	.083
Any non-PE/CPT group therapy, %, n	32.6	638	33.8	231	.564
Any non-F/P/S/V antidepressant, %,n	50.9	997	51.5	352	.798
Any anticonvulsant, %, n	20.6	403	21.5	147	.610
Any sedative/hypnotics, %, n	24.1	472	27.6	189	.066
Any opioid, %, n	20.8	407	21.1	144	.878
Any atypical antipsychotic, %, n	9.2	181	14.6	100	<.001
Any prazosin, %, n	19.1	375	18.6	127	.741
Any nicotine replacement, %, n	5.8	113	8.3	57	.019
Any naltrexone or Acamprosate, %, n	0.9	17	1.3	9	.307
Any opioid replacement therapy, %, n	0.6	11	0.9	6	.374

Abbreviations: CPT, cognitive processing therapy; F/S/P/V, Fluoxetine/Sertraline/Paroxetine/Venlafaxine; M, mean; MH, mental health; OEF/OIF/OND, Operations Enduring Freedom/Iraqi Freedom/New Dawn; OP, outpatient; PE, prolonged exposure; PTSD, post-traumatic stress disorder; SA, substance abuse; SD, standard deviation; TBI, traumatic brain injury.

point range of clinically meaningful improvement on the PCL.[28,29] At the same time, being in the substantial improvement group was associated with a much higher rate of loss of diagnosis plus a 10-point improvement (39.0% versus 16.8%), an outcome that is associated with increased quality of life.[30] This underscores the evidence that outcomes for patients in our two trajectory groups were appreciably different. However, with an AUC of 0.55, our model to predict membership in the substantial improvement group using available patient and treatment covariates was only slightly better than chance.

We were surprised to find that receiving EBT for PTSD was not a predictor of being in the substantial improvement group. In this dataset, having sufficient PCL measurement for trajectory analysis is essentially a proxy for receiving a high level of EBT, making it difficult to assess the effects of receiving versus not receiving guideline-concordant care on clinical trajectory. Patients in both groups who were prescribed EBAs received a mean of 9 to 10 weeks of treatment. This was in line with VA treatment guidelines at the time, which recommended that antidepressants be continued for at least 8 weeks when treating PTSD.[41] Patients in both groups received similarly high levels of individual EBPs during the 12-week trajectory period, both in terms of percent receiving PE and CPT and in terms of the mean number of sessions received. While we were unable to meaningfully predict trajectory based on available patient and treatment characteristics, unmeasured characteristics such as receipt of preferred treatment and treatment expectations could account for these differences.[42-44] Information regarding these factors is not available in the CDW.

Our findings in clinical practice regarding gender mirror the Watts et al meta-regression of published RCT data,[5] suggesting that men may not respond as well to available PTSD treatments as women. Given our approach, the finding on gender applies generally to treatments provided to men in our cohort during the trajectory period. However, a national evaluation of the VA PE implementation programme by Eftekhari et al[45] found a significantly poorer effect for men versus women (approximately 5 points on the PCL). Thus, the

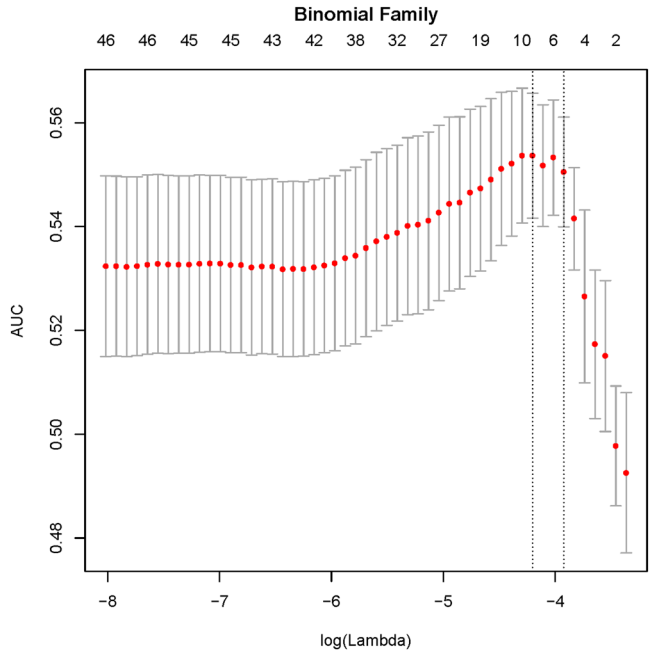

FIGURE 2 Least absolute shrinkage and selection operator (LASSO) cross validation results. The y-axis represents the area under the curve, or AUC

TABLE 3 Classifiers in final LASSO model, with bootstrapped CIs

Variable	Odds Ratio	95% CI	
		Lower	Upper
Men	0.76	0.58	0.96
Homeless	0.76	0.49	1.00
Headache disorder	0.96	0.77	1.00
Alcohol dependence	1.15	1.00	1.48
Non-PE/CPT individual psychotherapy sessions	1.02	1.00	1.05
Atypical antipsychotic	1.33	1.00	1.80
Nicotine replacement	1.09	1.00	1.53

Abbreviations: CI, confidence interval; LASSO, least absolute shrinkage and selection operator; PE/CPT, prolonged exposure/cognitive processing therapy.

finding of worse outcomes in men may also apply to men receiving specific PTSD treatments in clinical practice. Research determining why men experience less benefit with treatment is warranted. This could be due to underlying gender differences in the pathology of PTSD or in the suitability of available treatments for men. Such research could lead to helpful modifications of current treatments or the design of new treatments that address issues unique to men.

There are key limitations to this work. First, sufficient PCL measurement to be included in the trajectory analysis was only available on 0.5% of our parent cohort. Therefore, our findings may not generalize to the broader VA PTSD treatment population. Use of the VA electronic medical record to administer the PCL in routine practice became more common in 2008 after implementation of an electronic decision support tool that prompted administration of the PCL to patients with PTSD diagnoses,[24] with rapid uptake of the practice between 2008 and 2013.[7] The VA's measurement-based care initiative, which encourages the use of the PCL to help guide treatment decisions, may further accelerate this process. Therefore, future studies using more recent samples are likely to be more representative of the VA PTSD treatment population. Telephone-based assessments for a representative sample of VA patients initiating care for PTSD, such as those collected through the Veterans Outcome Assessment programme,[46] may also aid in the representativeness of studies assessing the effectiveness of routine VA care. Second, we may have decreased the proportion of patients participating in PCL measurement by examining only 1 year of care. Maguen et al[4] showed that it commonly takes up to 3 years following an initial VA PTSD diagnosis to receive an EBP. This is a critical consideration for future work using clinical data, as our study indicates EBP receipt drives the use of PCL measurement. Third, it is possible that EBPs were delivered with poor fidelity or that patients who were prescribed EBAs were not actually taking them. Measures of psychotherapy treatment fidelity and psychopharmacology treatment adherence were not widely used in clinical practice during the years we examined. Fourth, we did not account for treatment history before the index PTSD diagnosis. For example, while the cohort was designed to capture treatment during the initial year of PTSD care, it is possible that patients received multiple EBAs before their index PTSD diagnosis as these medications are frequently used for other conditions. Future work should account for longitudinal treatment history as prior treatment resistance could explain current lack of improvement.[31]

In conclusion, while we were unable to predict which VA PTSD treatments work the best and for whom in routine clinical practice, we report two highly relevant clinical findings. First, our work indicates that patients receiving a high level of PTSD care in the VA do achieve meaningful improvements in symptoms. This is important information as it indicates that routine PTSD care provided by the VA can effectively reduce PTSD symptoms. Second, we showed that men do not appear to benefit from available PTSD treatments as much as women in routine VA practice. This suggests that additional research to confirm our findings and to understand why men do not benefit as much from PTSD treatment is needed and should be a priory for the VA.

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CONFLICTS OF INTEREST

Dr Shiner reports no conflict of interest (COI). Dr Gui reports no COI. Ms Westgate reports no COI. Dr Schnurr reports no COI. Dr Watts reports no COI. Ms Cornelius reports no COI. Dr Maguen reports no COI.

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APPENDIX

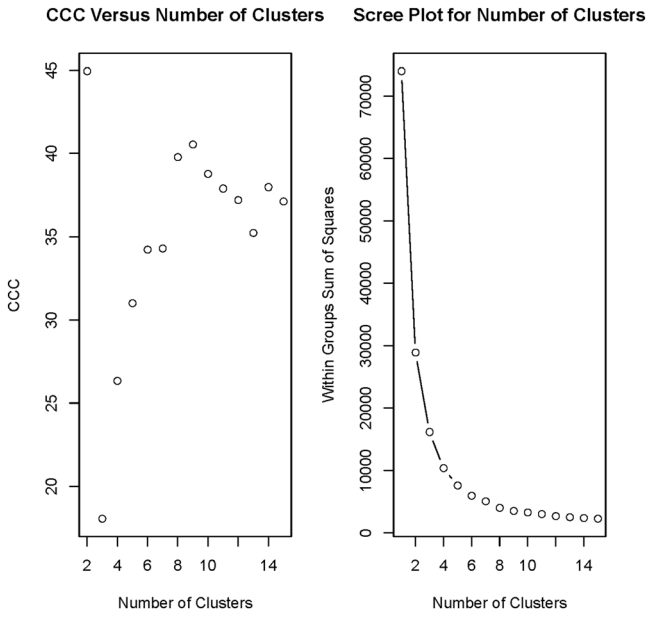

FIGURE A1 Cluster analysis results. Please note, Cubic Clustering Criteria is represented by CCC

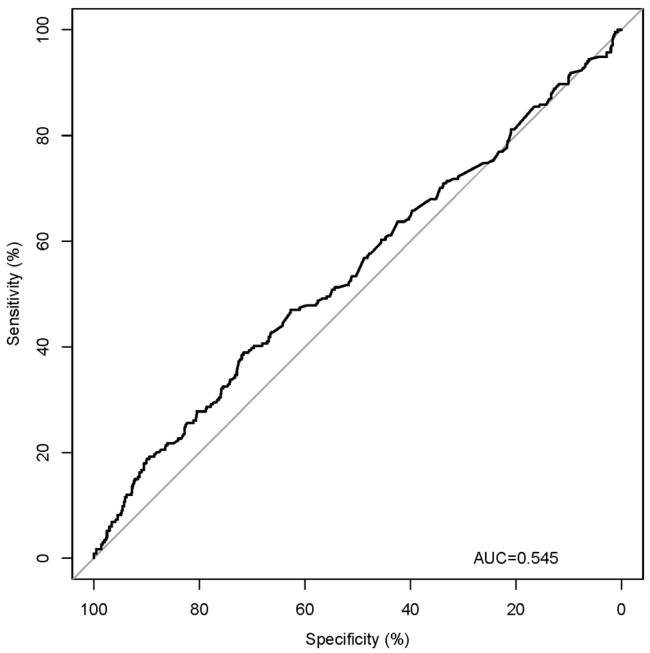

FIGURE A2 Receiver operating characteristics. Area under the curve is represented by AUC

Administration and Policy in Mental Health and Mental Health Services Research

Measurement Strategies for Evidence-Based Antidepressants for Posttraumatic Stress Disorder Delivery: Trends and Associations with Patient-Reported Outcomes

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Running head: MEASUREMENT STRATEGIES FOR EBA FOR PTSD DELIVERY

Measurement Strategies for Evidence-Based Antidepressants for Posttraumatic Stress Disorder Delivery: Trends and Associations with Patient-Reported Outcomes

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Abstract

We sought to develop a quality standard for the prescription of antidepressants for posttraumatic stress disorder (PTSD) that is both consistent with the underlying evidence supporting antidepressants as a treatment for PTSD and associated with the best levels of symptom improvement. We quantified antidepressant receipt during the initial year of PTSD treatment in a 10-year national cohort of Department of Veterans Affairs (VA) users who completed patient-reported outcome measurement as part of routine practice. We added progressively stringent measurement requirements. The most stringent requirement was associated with superior outcomes. Prescribing quality for PTSD in the VA was stable over time.

Keywords: Quality of Healthcare; Patient Reported Outcomes Measures; Comparative Effectiveness Research; Psychopharmacology; Stress Disorders, Posttraumatic

Measurement Strategies for Evidence-Based Antidepressants for Posttraumatic Stress Disorder Delivery: Trends and Associations with Patient-Reported Outcomes

Posttraumatic stress disorder (PTSD) is a mental health condition that sometimes follows exposure to a traumatic event (American Psychiatric Association, 2013). Symptoms include reexperiencing the trauma, avoidance of reminders of the trauma, hyperarousal, and negative cognitions. PTSD affects approximately 6% of the United States (US) population during their lifetime (Goldstein et al., 2016; Pietrzak, Goldstein, Southwick, & Grant, 2011). Rates are higher in combat or military-exposed populations such as veterans who use health services provided by the US Department of Veterans Affairs (VA; Holowka et al., 2014; Shiner, Drake, Watts, Desai, & Schnurr, 2012). Convergent findings from recent meta-analyses indicate that four antidepressant medications are effective treatments for PTSD, including the selective serotonin reuptake inhibitors (SSRI) fluoxetine, sertraline, and paroxetine, as well as the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine (Jonas et al., 2013; Watts et al., 2013). Randomized clinical trials supporting the efficacy of these four evidence-based antidepressants (EBAs) in the treatment of PTSD are 12 weeks in length (Jonas et al., 2013).

A series of national studies have been published about use of antidepressants for PTSD in routine VA practice. Mohamed and Rosenheck (2008) found that of 274,297 VA users with a PTSD diagnosis in the 2004 fiscal year, 71% (195,371) received at least one prescription for any antidepressant. Examining a similar time frame, Spoont, Murdoch, Hodges, and Nugent (2010) measured antidepressant initiation among a more restricted cohort of VA users with new PTSD treatment episodes by excluding those who previously received mental health treatment or antidepressants. Among 20,284 VA users with new PTSD treatment episodes in 2004 and 2005, 50% (10,127) received an antidepressant and 27% (5,487) received a 120-day or greater supply

of an antidepressant during the six months following their initial diagnosis. Finally, Abrams, Lund, Bernardy, and Friedman (2013) examined a cohort of 356,958 VA users with PTSD who regularly received medications from VA pharmacies in the 2009 fiscal year. Among this cohort, 66% received an SSRI or SNRI and 60% received a 90-day or greater supply of an SSRI or SNRI. The results of these three studies are not directly comparable due to differences both in cohort selection and outcome. Thus, these studies highlight how methodological choices may lead to variation in estimates about the application of PTSD treatment evidence in clinical practice.

Chassin, Loeb, Schmaltz, and Wachter (2010) proposed that to be valid, a quality measure must capture whether an evidence-based care process has actually been provided. Therefore, while measuring whether patients with PTSD receive an SSRI or SNRI is an improvement over measuring whether they receive any antidepressant, a measure of whether they receive fluoxetine, sertraline, paroxetine, or venlafaxine would more closely reflect an evidence-based process. Similarly, while measuring treatment duration is an improvement over examining the receipt of any prescription, it would also be important to determine whether patients received the same antidepressant doses that were tested in clinical trials for PTSD. As these four EBAs are prescribed for many indications other than PTSD, it also would be important to make a stronger determination of whether they are prescribed "for PTSD." While prescription data is not typically associated with an indication, the Spoont et al. (2010) strategy of examining patients with new diagnoses of PTSD who have not previously received an antidepressant excludes prescriptions that are likely to be for indications other than PTSD. Similarly, the Spoont et al. (2010) 120-day strategy has advantages and disadvantages when compared to the Abrams et al. (2013) 90-day strategy. A 120-day supply would necessitate that patients request a

refill (as the VA dispenses a maximum supply of 90 days), and prior studies demonstrate that requesting a refill is associated with higher rates of medication adherence among VA users (Osterberg & Blaschke, 2005). However, this creates a quality standard that is more stringent that the evidence supporting the use of treatment, as 120 days is significantly longer than the typical 12-week (84 day) clinical trial. Finally, none of the existing studies examine follow-up care. Clinical trials establishing the efficacy of psychotropic agents provide the same amount of follow up care to patients randomized to active agent or placebo, so cannot be used to determine the optimal follow-up regimen.

Due to methodological limitations, available research on use of EBAs for PTSD may paint an overly optimistic picture of current practice, potentially obscuring an opportunity to improve PTSD care. Our goal was to determine whether there are potentially correctable gaps in EBA treatment of PTSD in terms of choosing the correct antidepressants, dosing, treatment duration, and follow-up care. Our specific objectives were to: (1) measure the delivery of EBAs for PTSD to a national cohort of Veterans initiating PTSD care; (2) determine longitudinal trends in EBA for PTSD delivery according to potential quality measures; and (3) to determine whether quality standards that more stringently reflect the evidence supporting EBA use are associated with superior outcomes.

Method

Data Source

We used the VA corporate data warehouse (CDW) to identify patients with new PTSD treatment episodes from fiscal year 2004 through fiscal year 2013. We obtained patient demographic information as well as encounter, diagnostic, and pharmacy data from the CDW. The Dartmouth College Committee for the Protection of Human Subjects, the White River

Junction VA Medical Center Research and Development Committee, and VA National Data Systems approved this study.

Patients

We included VA users who received a primary diagnosis of PTSD at two or more outpatient encounters, at least one of which occurred in a mental health setting, over the course of 90 days between October 1, 2003 and September 30, 2013, and had not met this criterion during the prior two years. We examined one year of treatment receipt following the first diagnosis of the two qualifying diagnoses. This was called the "index PTSD diagnosis." When patients met the cohort inclusion criteria multiple times over the 10-year period, only their first episode was included. This resulted in a cohort of 731,520 patients. This cohort has been previously described elsewhere (Shiner, Leonard Westgate, Bernardy, Schnurr, & Watts, 2017; Shiner, Leonard Westgate, Harik, Watts, & Schnurr, 2016; Shiner, Westgate, Bernardy, Schnurr, & Watts, 2017).

Antidepressant Receipt

We examined all medications dispensed by VA pharmacies during the year following the index PTSD diagnosis. Antidepressant drug names were classified into categories for individual agents and an overall category. The antidepressant drug class label was used to confirm our coding. We created categories of antidepressant receipt in four ways. First, we determined whether patients received any antidepressant. Second, we determined the most commonly prescribed antidepressant and determined whether patients received it. Third, we determined whether patients received an antidepressant recommended by the 2010 clinical practice guideline for PTSD from the US Department of Veterans Affairs and Defense (VA/DoD CPG; Friedman, Lowry, & Ruzek, 2010), which were in place at the time care was delivered to patients in our

cohort. The 2010 VA/DoD CPG gives A- or B-level recommendations to SSRI/SNRI antidepressants, mirtazapine, nefazodone, amitriptyline, imipramine, and phenelzine. Fourth, we determined whether patients received any of the four EBAs for PTSD, including fluoxetine, paroxetine, sertraline, and venlafaxine.

Covariates

We developed three groups of covariates. First, we examined patient characteristics including age, gender, race, military service era, rurality, military-related exposures (e.g., combat and sexual trauma), and medical and psychiatric comorbidities. Second, we examined service use characteristics including prior use of antidepressants, outpatient visits, emergency department visits, and admissions. For prior use of antidepressants, we assessed whether patients received any antidepressant prescriptions in the 2 years prior to their index PTSD diagnosis. Outpatient visits included visits to specialized PTSD clinics, general mental health clinics, substance abuse clinics, and primary care clinics. We assessed whether patients had concurrent evidence-based psychotherapy for PTSD, including prolonged exposure or cognitive processing therapy, using an algorithm to classify psychotherapy notes that has been described elsewhere (Maguen et al., 2018), and considered eight or more sessions to be a minimally adequate trial (Hale, Bohnert, Ganoczy, & Sripada, 2019). Emergency department visits included emergency department visits for a psychiatric indication. Admissions included stays included those to acute mental health inpatient wards, residential PTSD treatment programs, or residential substance abuse programs. Third, we examined prescribing clinician characteristics. Patients were assigned a primary prescribing clinician based on the clinician who wrote the plurality of their psychotropic prescriptions. Primary prescribing clinicians were characterized by age, gender, professional background, and service section. Professional background included physician,

physician assistant, nurse practitioner, and pharmacist. Service section included specialized PTSD, general mental health, substance abuse, primary care-mental health integration clinics, and primary care. Because prescribing clinicians may work across multiple service sections, we calculated the percentage of time they spend seeing PTSD patients in various settings. This was based on our assumption that prescribing clinicians who spend a higher percentage of their time in specialized PTSD settings may bring increased knowledge and experience in treating PTSD, even when seeing patients in non-specialized settings.

Measures of Prescribing Quality

We examined prescribing quality among the sub-cohort of patients who had not received an antidepressant prescription in the two years prior to their index PTSD diagnosis. For patients who received a new prescription of any of the four EBAs for PTSD on or after their index PTSD diagnosis, we determined whether they received an adequate treatment, which we defined as a 12-week or more continuous period where patients received the medication at an adequate dose. We adjusted days' supply of prescription fills for discontinuations occurring prior to the calculated end of a prescription fill. We excluded prescriptions that were never filled, that were filled by the pharmacy and never picked up by the patient, or mailed back to the pharmacy because they were undeliverable. Also excluded were fills provided as part of research protocols and an insignificant number of liquid-based pharmacy orders. Because 12-week clinical trials frequently include titration periods (Jonas et al., 2013), we required a dose that was equal to or higher than the typical target dose in RCTs supporting the use of these treatments for at least the final 8 weeks. We standardized and interpreted titration instructions using regular expressions. We ignored initial titration instructions when they were erroneously carried forward to a subsequent fill, but did capture new changes to instructions such as dose increases and tapering

instructions when present in a subsequent fill. Target doses were fluoxetine 20 mg daily (Martenyi, Brown, & Caldwell, 2007; Martenyi, Brown, Zhang, Prakash, & Koke, 2002; Martenyi & Soldatenkova, 2006; van der Kolk et al., 1994; van der Kolk et al., 2007), paroxetine 20 mg daily (Marshall, Beebe, Oldham, & Zaninelli, 2001; Tucker et al., 2001), sertraline 100 mg daily (K. Brady et al., 2000; K. T. Brady et al., 2005; J. Davidson, Rothbaum, et al., 2006; J. R. Davidson, Rothbaum, van der Kolk, Sikes, & Farfel, 2001; Friedman, Marmar, Baker, Sikes, & Farfel, 2007; Tucker et al., 2004; Zohar et al., 2002), and venlafaxine 150 mg daily (J. Davidson, Baldwin, et al., 2006; J. Davidson, Rothbaum, et al., 2006). We similarly used regular expressions to interpret instructions regarding how different strengths of the same EBA from multiple pill bottles were to be combined (e.g. 150 mg capsules of Venlafaxine XR are commonly combined with 75 mg capsules of Venlafaxine for a total daily dose of 225 mg daily, but are also sometimes prescribed as 150 mg and 75 mg doses on alternating days). Use of and dose of each EBA over the 365 days following the index PTSD diagnosis was represented as an array, so that medication coverage could be aligned with the receipt of other services.

In addition to dose and days of coverage, we examined several additional possible quality measures. Firstly, we added a requirement for at least one refill, as an indication that the patient was consuming the medication. For patients who received an initial prescription that covered 84-90 days, we allowed up to the end of week 14 for receipt of a refill. Secondly, we added a requirement that patients had at least one in person or video-based follow-up visit during the adequate treatment trial, as an indication that the medication could have been adjusted if there was a problem. Eligible clinicians for follow-up visits included the original prescribing clinician, the plurality prescribing clinician, or any mental health clinician with prescription privileges. Thirdly, we expanded the follow-up requirement to include three encounters with an

eligible clinician during the adequate treatment trial, at least one of which was in person or video-based (the other two visits could be telephone calls). We chose our follow-up standards to be consistent with a VA performance measure for antidepressant medication management in place at the time patients in this cohort underwent treatment (Shiner, Watts, Traum, Huber, & Young-Xu, 2011).

Patient-Reported Outcomes Assessment

Availablity of structured data from patient-reported outcome measurement using the PTSD Checklist (PCL; Weathers, Litz, Herman, Huska, & Keane, 1993) began to increase in FY08 (Shiner et al., 2018). Therefore, we obtained available PCL data for the FY08-13 portion of the cohort. During these years, the VA used the version of the PCL corresponding to PTSD diagnostic criteria in the fourth version of the Diagnostic and Statistical Manual of Mental Disorders, called DSM-IV (American Psychiatric Association, 2000). This version of the PCL was a 17-item measure with each item rated on a five-point Likert-type scale, resulting in total scores ranging from 17 through 85 (Weathers et al., 1993). Respondents were asked to rate how much they are bothered by each symptom over the last month. Symptom presence was determined by a response of "moderately" or greater (Weathers et al., 1993). Therefore, the tool could be used to determine whether patients met minimal symptomatic criteria for PTSD according to DSM-IV (one re-experiencing symptom, three avoidance and numbing symptoms, and two hyperarousal symptoms). Clinically meaningful improvement has been previously defined as a decrease of 10 points or more (Monson et al., 2008). A clinically meaningful improvement in PTSD symptoms plus no longer meeting diagnostic criteria for PTSD has been shown to be an important marker of improved quality of life (Schnurr & Lunney, 2016).

Analysis

Our analysis plan was divided into descriptive and causal elements. For descriptive analyses using the entire FY04-13 cohort, we summarized cohort characteristics and compared patients who received antidepressants with those who did not using t-test or χ^2 analysis, as appropriate. We described antidepressant receipt for the entire cohort during each fiscal year and for the overall 10-year period. We then focused on antidepressant initiation by excluding patients who received antidepressants in the 2 years prior to their index PTSD diagnosis and then recalculated initiation rates for any of and each of the EBAs for PTSD for each individual fiscal year and for the overall 10-year period. We progressively added the measures of prescribing quality described above to this sub-cohort.

For causal analyses using patients from the FY08-13 portion of the cohort, we identified patients who initiated psychotherapy at progressively higher levels of adherence to our "quality" measures (12 weeks at an adequate duration, plus adequate dose, plus a refill, plus 1 follow-up, plus 3 follow-ups) and had concurrent symptoms measurement using the PCL (defined below). When patients received multiple EBAs during the initial year, we chose the first trial. We created orthogonal comparison groups by including patients only in the longitudinally earliest (first during treatment year) quality standard that they met. Patients who initiated care that met multiple quality standards on the same day were assigned to the strictest standard met on that day. From this group, we selected patients who had a minimum of a PCL score within 2 weeks of the start of treatment (baseline) and within 2 weeks of the 12-week point (follow-up). To ensure patients had active PTSD symptoms at baseline, we required that they meet DSM-IV symptomatic criteria on their baseline PCL. When there were multiple PCL scores meeting our baseline criterion, we selected the measure closest to the start of treatment. When there were multiple PCL scores meeting our follow-up criterion, we selected the measure closest the 12-

week point. We calculate two change measures from baseline to follow-up: (1) mean PCL change, and (2) percentage with "loss of diagnosis," which included both no longer meeting symptomatic criteria for PTSD plus experiencing a meaningful decrease in symptoms of 10 points or more.

Following a procedure developed in prior work to assess pre/post changes (Shiner et al., 2018), we examined both the raw change in PTSD symptoms among those with measurement and the patient characteristic-weighted mean change, as well as the percentage of patients achieving our loss of diagnosis criterion. Given that we were comparing five progressively strict standards (12 weeks at an adequate duration, plus adequate dose, plus a refill, plus 1 follow-up, plus 3 follow-ups) comprising ten comparisons (each standard versus all other standards), we planned a conservative Bonferroni-corrected alpha of $p<0.005$ to avoid type I error. We used inverse propensity of treatment weighting (IPTW; Stuart, 2010) to balance covariates that have a plausible association with the outcome. These covariates included all patient, service use, and primary prescribing clinician covariates described above as well as days from index PTSD diagnosis to EBA start, baseline PCL score, days from baseline PCL to day 1, days from follow-up PCL to day 84, and fiscal year treated. We estimated propensity scores with multinomial logistic regression using generalized booster effects (McCaffrey et al., 2013), in which case the dependent variable is an indicator for the quality standard met and the independent variables are an antiparsimonious specification of covariates. Using these propensity scores, we weighted participants in order to balance the covariate distribution. In balancing almost 50 covariates, a Bonferroni correction would indicate a corrected alpha of $p<0.001$. However, we conservatively maintained an alpha threshold of $p<0.01$ for significant differences to avoid type II error. Therefore, covariates that continued to differ at the $p<0.01$ threshold after IPTW were included

as covariates in models of change in PTSD symptoms. We assessed the potential contribution of unmeasured confounding on significant pre/post comparisons by calculating E-values, which indicate the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the exposure and the outcome, conditional on the measured covariates, to fully explain away a specific exposure-outcome association (Haneuse, VanderWeele, & Arterburn, 2019; VanderWeele & Ding, 2017).

In addition to our pre/post measures, we performed a repeated measures model that included all PCL measurements between baseline and follow-up. We used a generalized linear mixed model (GLMM) to account for both within-person and across-person variability. We compared changes in PTSD symptom during the time treatment was delivered, including a time by treatment interaction which measures the change in slope over time among the tree treatment groups. The model was weighted by the inverse of the propensity scores and adjusted for any unbalanced covariates. We performed data management in SAS version 9.4 (SAS Institute), and developed causal models in R version 3.5.0 (R core team). This included IPTW models created using the R twang package (Ridgeway, McCaffrey, Morral, Burgette, & Griffin, 2017), and models to detect unmeasured confounding using the R evalue package (Mathur, Ding, & VanderWeele, 2018).

Results

Of the 731,520 patients in our cohort, 83.4% (n=609,808) filled at least one antidepressant prescription during their first year of PTSD treatment. Patients who did and did not fill an antidepressant prescription differed on almost every variable (Table 1), although the differences detected were typically very small and only significant due to the large sample size. Most prominently, those who filled and antidepressant prescription were more likely to have

psychiatric and medical comorbidities (in addition to PTSD), and also higher levels of VA service-connected disability. They were also far more likely to have received an antidepressant in the two years prior to their index PTSD diagnosis and received more visits, admissions, and residential treatment in the year following their index PTSD diagnosis. They were slightly less likely to receive a minimally adequate trial of evidence-based psychotherapy. Primary prescribing clinicians were most commonly male, physicians, and working in the general mental health service section.

In the overall cohort, use of antidepressants, including those recommended in the 2010 VA/DoD CPG for PTSD, decreased slightly over the 10-year period of examination (Table 2). For example, in FY04-05 86.6% filled any antidepressant while 78.9% filled a CPG-recommended antidepressant. By FY12-13, those numbers had steadily dropped to 80.6% and 72.0%, respectively. Use of an EBA for PTSD was very similar at the start and end of the 10-year period of observation. In FY04-05, 54.0% filled an EBA and this increased slightly to 54.7% in FY12-13. However, there was an approximately 10% drop in EBA use across the middle years from FY06-FY11. The most sustained decreases in EBA fills were in fluoxetine and paroxetine. Sertraline was the most commonly filled EBA. After a brief dip from 25.8% in FY04-05 to 17.7% in FY06-07, sertraline fills recovered and increased to 33.4% by FY12-13. Venlafaxine fills held steady between 9.0% and 9.9% for most of the period of observation, but increased to 12.2% in FY12-13. Notably, trazodone, which was not recommended for PTSD in the 2010 VA/DoD CPG, was the most commonly filled antidepressant across all years, with over a third of patients filling trazodone prescriptions.

When we applied quality standards to medication fills among the 52.2% (n=381,698) of patients initiating antidepressants after their index PTSD diagnosis, the number meeting those

standards decreased as the standards became more stringent (Table 3). For example, while 35.4% received at least one EBA fill in their first year of treatment, the figure dropped to 19.6% when we add an adequate duration requirement, 14.8% when we add an adequate dose requirement, 12.7% when we add a refill requirement, 9.7% when we add a one-follow-up requirement, and 4.6% when we add a three-follow-up requirement. In general, added requirements led to similar degradations in treatment adequacy across individual EBAs with the exception of sertraline and venlafaxine, which were more highly impacted by dosing requirements than fluoxetine and paroxetine. With the exception of a dip from 4.4% in FY04-05 to 3.7% in FY06-07, the percentage of patients meeting our most stringent standard held steady over time before increasing to 6.0% in FY12-13. (Appendix 1).

A small number of patients from the FY08-13 cohort who met our increasingly restrictive quality standards had PCL measurement aligned with the start of treatment and the 12-week point, so were included in analyses comparing outcomes among patients who met increasingly strict quality standards. Among the 52,907 patients who received an adequate duration of EBA from FY08-13, 2.0% (1,068) met our PCL-based inclusion criteria. Patients with the required PCL measurement differed from others receiving an adequate dose and duration of EBA in many ways (Table 4). Notably, they were almost 8 years younger, over 30% more likely to be OEF/OIF/OND Veterans, and had half the level of medical comorbidity as measured by the Charleston index, while at the same time having higher rates of depression, anxiety, TBI, alcohol use disorders, and opioid use disorders. Additionally, they had far higher rates of inpatient, residential, and outpatient services use, including a five-fold higher rate of receiving a minimally adequate trial of evidence-based psychotherapy for PTSD. Finally, patients who met our PCL-

based inclusion criteria were more likely to be treated by prescribing clinicians who work specialized PTSD clinics rather than general mental health clinics.

It was rare for patients who met our PCL-based inclusion criteria to have an adequate dose and duration without at least one follow-up, so the "adequate dose and duration" (n=90) as well as the "adequate dose and duration plus refill" (n=47) groups were collapsed into an "adequate dose and duration plus/minus refill" in our causal analysis. Thus, there were six rather than ten comparisons in our pre/post analyses so the Bonferroni-corrected alpha was raised from $p<0.005$ to $P<0.008$. Among patients with measurement, those that met the strictest quality criteria were different from one or more of the less strict groups in many ways (Appendix 2). Most notably patients in the strictest group started EBAs earlier in their index year of treatment and were younger, more likely to be women, less likely to be married, and less likely to be rural. They had higher rates of alcohol and other drug use disorders, and attended more outpatient mental health visits and outpatient substance abuse visits. They were also more likely to receive psychiatric care in the emergency room, acute inpatient mental health, and residential treatment settings. Applying the IPTW procedure resolved these differences (Appendix 3), but one difference between the quality groups remained: those in the one follow-up group had fewer substance abuse visits than patients in the other groups. This unbalanced variable was used as a covariate in weighted analyses.

In both the unweighted and weighted pre/post comparisons, there were no significant differences in either our continuous outcome of change in PCL or our categorical outcome of 10-point drop in PCL plus loss of diagnosis (Table 5). Across groups in the weighted analysis, continuous change in PCL ranged from -5.4 points to -7.0 points while 10-point drop in PCL plus loss of diagnosis ranged from 10.7% to 17.3%. Because there were no significant pre/post

differences between quality groupings, we did not compute E-values to assess the robustness of the finding. In the repeated measures analysis, the least strict standard was modeled as a main effect, with an intercept of 64.4 points on the PCL. Across all groups, only the strictest standard was associated with a small but statistically superior outcome of -1.8 points on the PCL (t=-2.0, p=0.045). No interaction terms between time and quality groupings were significant.

Discussion

While most patients received an antidepressant during the first year of a VA PTSD treatment episode (83.4%), many fewer received an EBA for PTSD (47.8%). Among the sub-cohort of patients who were not already prescribed an antidepressant in the two years prior to their index PTSD diagnosis, only 35.4% received an EBA. As proposed quality standards based on the literature accounted for adequate dose and duration, the proportion who received adequate care dropped to less than 15%. If basic follow-up standards were applied, including receiving refills of the medications and having three appropriate follow-up visits over the initial 12 weeks treatment, the proportion receiving evidence-based care fell to less than 5%. Among those initiating an EBA, sertraline was the most commonly used medication (20.6%), and the rate of use of other EBAs was similar and ranged from 4.9% to 8.3%. Among patients initiating an EBA and meeting our PCL-based criteria for inclusion in causal analyses, there was a statistically significant advantage to meeting our strictest quality standard for EBA prescribing, which included receiving an adequate dose and duration of fluoxetine, sertraline, paroxetine, or venlafaxine plus a refill and three appropriate follow-ups, when compared to receiving an adequate duration alone. However, this effect was small at just under two points on the PCL over the course of 12 weeks, and was not consistent with findings in the pre/post analysis. This indicates that the results should be taken with caution and are less than a complete endorsement

of the standard. Regardless, given that this standard is consistent with the underlying evidence for EBA treatment as well as more general guidelines for follow-up after the initiation of an antidepressant, future researchers should consider using and improving upon our work.

While the high overall rate of antidepressant use in this cohort is consistent with findings with findings by Mohamed and Rosenheck (2008), and the high rate of SSRI/SNRI use is consistent with findings by Abrams et al. (2013), treatment adequacy for newly-initiated agents appears to be lower than described by Spoont et al. (2010). Adding any restrictions (duration, dosing, refills, follow-ups) to the requirement to prescribe antidepressants that are effective for PTSD (rather than any antidepressant) drives the percentage of patients meeting the measure to below 20% (and as low as 4.6%) over the subsequent year. This is in contrast to the Spoont et al. (2010) finding of 27% initiating an adequacy supply of any antidepressant over the six months following a new diagnosis of PTSD. The finding by Spoont et al. (2010) is likely affected by their inclusion of all antidepressants rather than an exclusive focus on EBAs for PTSD.

Our findings indicate major opportunities to improve antidepressant prescribing as a way to ameliorate PTSD symptoms in the VA. When considering the need to improve prescribing for PTSD, our focus on fluoxetine, sertraline, paroxetine, and venlafaxine is more limited than the A- and B- level recommendations in the 2010 VA/DoD CPG in place at the time this cohort was treated (Friedman et al., 2010). These four EBAs are now the only medications for PTSD recommended in the most recent 2017 VA/DoD CPG (The Management of Posttraumatic Stress Disorder Work Group, 2017). Given this design, our work is applicable for improving prescribing practices moving forward. The depression literature indicates that improving antidepressant prescribing as a way to improve outcomes often requires changes that are at the same time well-organized and locally relevant (Dietrich et al., 2004; Shiner et al., 2010; Trivedi

et al., 2004). Efforts to apply lessons from improving depression care to improving PTSD care have been mixed (Engel et al., 2016; Fortney et al., 2015; Schnurr et al., 2013). Therefore, awareness regarding the effective medications and their use is necessary but unlikely to be sufficient to improve outcomes for patients with PTSD receiving antidepressant treatment (Watts, 2016).

Across all groups, the mean 12-week pre/post change in PTSD symptoms was modest at a 5.4 to 7.0-point decrease on the PCL. This change is not directly comparable results from RCTs of antidepressants for PTSD, which do not typically report PCL outcomes (Watts et al., 2013). A recent RCT of three PTSD treatment strategies in Veterans at four VA and non-VA sites by Rauch, Kim, et al. (2018) showed a dramatically better response in the medication treatment group. Patients randomized to manualized enhanced medication management with sertraline for PTSD had a mean 12-week pre/post change of 13.4 points on the PCL. The enhanced medication management protocol was designed to ensure that patients randomized to sertraline received a similar amount of time, psychoeducation, and clinician support as patients receiving psychotherapy (Rauch, Simon, et al., 2018). While patient factors could account for the less impressive results in our cohort, the Rauch, Kim, et al. (2018) results open the possibility of achieving better PTSD outcomes through improved prescribing practices in the VA.

There was an unusual trend whereby any use of EBAs decreased significantly during the middle years of our period of observation before returning to previous levels in the last two years. In previously-published analyses looking more broadly at psychotropic prescribing in this cohort, it appears that there may have been substitution from increased use of other classes of medications that are not clearly effective for PTSD such as anticonvulsants (Shiner, Westgate, et al., 2017), and that the rebound in EBA use coincided with a drop in atypical antipsychotic and

benzodiazepine use (Krystal et al., 2017). While increases in anticonvulsant use persisted throughout the years of examination, the reemergence of EBA use in the later years may have been driving by policies intended to decrease atypical antipsychotic and benzodiazepine use, which coincided with efforts that focused on substituting guideline-concordant treatments for these agents (Bernardy et al., 2013; Lund, Abrams, Bernardy, Alexander, & Friedman, 2013).

While this study makes a critical contribution to this literature by leveraging electronic medical record data to understand prescribing practices for PTSD in the VA, there are limitations to our work. First, we used pharmacy data including fills and refills to assess mediation receipt. Without directly monitoring or even talking to patients, it is not possible to tell whether they took the EBAs as prescribed. For example, if patients were not adherent to their medication instructions, it might account for low level of improvement associated with EBA receipt. Second, only 2% of patients receiving at least an adequate duration of an EBA had PCL measurement that was aligned with weeks one and twelve, making them eligible for inclusion in the causal analysis. Patients who met our PCL-based inclusion criteria differed from other patients in many important ways. Thus, our findings may not be generalizable across VA patients. As use of measurement-based care increases in routine VA practice (Shiner et al., 2018), our hope is that comparative effectiveness analyses can be more representative of key groups such as older veterans. Third, our causal analyses focused on new antidepressant prescriptions among patients initiating PTSD treatment episodes. It is possible that Veterans who have been in VA PTSD treatment for many years realize even less benefit when switching to an EBA from other agents. Thus, it is not currently clear that optimizing EBA management would represent a way forward Veterans with chronic treatment-resistant PTSD (Sippel, Holtzheimer, Friedman, & Schnurr, 2018). Future studies should use a longitudinal, rather than

cross-sectional window of examination in order to account more comprehensively for prior treatment resistance.

In summary, we have measured prescribing practices for PTSD in routine VA practice with a greater degree of granularity than in previous studies, and have shown that the quality may be worse than previously estimated. Furthermore, even when examining outcomes for patients who receive the highest quality of care that we can measure using medical records data, outcomes appear to have substantial room for improvement. Many unmeasured factors could account for our findings and an organized practice-based effort is needed to understand these factors in order to initiate changes that will close the gap between the anticipated and observed benefit of a very commonly delivered modality of treatment for PTSD.

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Table 1: VA Users with New Episodes of PTSD Care from 2004-2013, by Receipt of an Antidepressant Prescription

	Overall (731,520)	Category: Received Antidepressant (609,808)	Category: Did Not Receive Antidepressant (121,712)
Patient Characteristics			
Age, M (SD)**	49.9 (15.4)	49.7 (15.1)	51.0 (16.6)
Women, % (n)**	8.5 (61,853)	8.7 (53,314)	7.0 (8,539)
Married, % (n)**	53.2 (389,262)	53.0 (323,106)	54.4 (66,156)
White Non-Hispanic, % (n)**	62.6 (457,673)	62.8 (382,798)	61.5 (74,875)
OEF/OIF/OND Veteran, % (n)**	28.5 (208,769)	28.1 (171,572)	30.6 (37,197)
Rural, % (n)**	35.3 (258,177)	35.8 (218,231)	32.8 (39,946)
Combat Exposure, % (n)	32.8 (239,686)	32.8 (199,881)	32.7 (39,805)
Sexual Trauma while in Military, % (n)**	9.2 (67,024)	9.5 (57,929)	7.5 (9,095)
VA Disability Level 70% or Greater, % (n)**	59.0 (431,632)	60.6 (369,635)	50.9 (61,997)
Charleson Comorbidity Index 1 or greater, % (n)**	24.4 (178,575)	25.4 (154,825)	19.5 (23,750)
Psychotic Disorders, % (n)**	5.7 (41,789)	6.0 (36,385)	4.4 (5,404)
Bipolar Mood Disorders, % (n)**	7.2 (52,596)	7.5 (45,632)	5.7 (6,964)
Depressive Mood Disorders, % (n)**	65.5 (478,763)	70.7 (430,956)	39.3 (47,807)
Non-PTSD Anxiety Disorders, % (n)**	34.5 (252,107)	36.1 (220,116)	26.3 (31,991)
Traumatic Brain Injury, % (n)**	8.6 (62,936)	8.8 (53,784)	7.5 (9,152)
Alcohol Use Disorders, % (n)**	27.1 (198,166)	28.6 (174,474)	19.5 (23,692)
Opioid Use Disorders, % (n)**	3.7 (27,175)	4.1 (24,846)	1.9 (2,329)
Other Drug Use Disorders, % (n)**	19.7 (144,350)	21.0 (128,142)	13.3 (16,208)
Service Use Characteristics			
Prior Antidepressant Use (2 years), % (n)**	47.8 (349,822)	55.8 (340,336)	7.8 (9,486)
Adequate Trial of EBP for PTSD, % (n)**	3.0 (22,144)	2.9 (17,865)	3.5 (4,279)
PTSD Outpatient Clinical Team Use, % (n)**	34.9 (255,151)	34.7 (211,748)	35.7 (43,403)
Outpatient Mental Health Visits, M(SD)**	12.6 (15.1)	13.2 (15.5)	9.5 (12.3)
Outpatient Substance Abuse Visits, M(SD)**	3.0 (13.1)	3.3 (13.6)	1.7 (9.9)
Outpatient Primary Care Visits, M(SD)**	3.5 (3.5)	3.6 (3.6)	2.7 (3.0)
ED Visit for Psychiatric Indication, % (n)**	6.4 (46,616)	7.1 (43,171)	2.8 (3,445)
Acute Mental Health Inpatient Admission, % (n)**	6.6 (48,531)	7.5 (45,915)	2.2 (2,616)
Residential PTSD Admission, % (n)**	2.4 (17,278)	2.7 (16,265)	0.8 (1,013)
Residential Substance Abuse Admission**	2.7 (19,696)	3.0 (18,470)	1.0 (1,226)
Primary Prescribing Clinician Characteristics			
Age, M (SD)	-	52.2 (10.7)	-
Woman, % (n)	-	39.4 (239,988)	-
Physician, % (n)	-	77.6 (473,427)	-
Physician Assistant, % (n)	-	4.1 (25,248)	-
Nurse Practitioner, % (n)	-	17.3 (105,338)	-
Pharmacist, % (n)	-	0.6 (3,814)	-
Percentage of Time Seeing PTSD Patients in Various Settings	-	-	-
PTSD Service Section (PCT or residential), M (SD)	-	11.8 (27.8)	-
Substance Abuse Service Section, M (SD)	-	2.4 (12.0)	-
Comorbid PTSD Substance Abuse Service Section, M (SD)	-	0.1 (1.7)	-
General Mental Health Service Section, M (SD)	-	61.7 (42.5)	-
Integrated Care Service Section, M (SD)		4.5 (15.6)	
Primary Care Service Section, M (SD)		13.2 (30.4)	

Note. VA=United States Department of Veterans Affairs; PTSD=Posttraumatic Stress Disorder; M=mean, SD=standard deviation; OEF/OIF/OND=Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn, EBP=Evidence-Based Psychotherapy; *p<0.05, **p<0.001

Table 2: Antidepressant Medication Receipt in the Year Following Initial PTSD Diagnosis

Fiscal Year	2004 – 2005	2006 – 2007	2008 – 2009	2010 – 2011	2012 – 2013	Overall
New PTSD Episodes	111,828	128,652	160,444	168,771	161,825	731,520
Number of ADs, M (SD)	2.1 (1.0)	2.0 (1.0)	2.0 (1.0)	2.0 (1.0)	2.0 (1.0)	2.0 (1.0)
Any Antidepressant	86.6% (96,887)	85.2% (109,576)	83.9% (134,635)	81.9% (138,203)	80.6% (130,507)	83.4% (609,808)
Trazodone	36.8% (41,187)	35.6% (45,777)	34.5% (55,342)	33.4% (56,388)	32.9% (53,210)	34.4% (251,904)
2010 VA/DoD CPGs	78.9% (88,202)	76.9% (98,870)	75.6% (121,313)	73.7% (124,429)	72.0% (116,581)	75.1% (549,395)
SSRI or SNRI	73.1% (81,732)	71.3% (91,737)	70.2% (112,604)	68.3% (115,244)	66.4% (107,424)	69.5% (508,741)
Mirtazapine	13.5% (15,142)	13.6% (17,488)	14.2% (22,791)	14.5% (24,454)	14.6% (23,574)	14.1% (103,449)
Nefazodone	1.2% (1,384)	0.4% (562)	0.2% (365)	0.1% (209)	0.1% (137)	0.4% (2,657)
Amitriptyline	7.3% (8,111)	6.2% (7,955)	5.5% (8,808)	4.7% (8,004)	4.6% (7,518)	5.5% (40,396)
Imipramine	0.4% (501)	0.4% (480)	0.3% (488)	0.3% (425)	0.2% (313)	0.3% (2,207)
Phenelzine	0.0% (32)	0.0% (28)	0.0% (17)	0.0% (19)	0.0% (17)	0.0% (113)
EBA for PTSD	54.0% (60,365)	43.8% (56,349)	43.4% (69,643)	44.2% (74,608)	54.7% (88,509)	47.8% (349,474)
Fluoxetine	15.9% (17,789)	14.1% (18,090)	11.6% (18,615)	10.7% (18,077)	12.5% (20,300)	12.7% (92,871)
Paroxetine	11.4% (12,723)	8.7% (11,173)	6.6% (10,616)	5.8% (9,749)	6.9% (11,101)	7.6% (55,362)
Sertraline	25.8% (28,817)	17.7% (22,812)	22.6% (36,194)	24.7% (41,681)	33.4% (54,013)	25.1% (183,517)
Venlafaxine	9.9% (11,082)	9.7% (12,500)	9.0% (14,385)	9.7% (16,311)	12.2% (19,739)	10.1% (74,017)

Note. PTSD=Posttraumatic Stress Disorder; AD=Antidepressant; M=Mean; SD=Standard Deviation; VA/DoD CPG=Departments of Veterans Affairs and Defense Clinical Practice Guideline for PTSD; EBA=Evidence-Based Antidepressant

Table 3: Antidepressant Initiation in the Year Following Initial PTSD Diagnosis among 381,698 Patients with No Antidepressant Fills in the 2 Years Prior to PTSD Diagnosis, Fiscal Years 2004-2013 (Yearly Trends in Appendix 1)

Quality Standard	Any Receipt	Adequate Duration	Plus Adequate Dose	Plus Refill	Plus 1 Follow-Up	Plus 3 Follow-Ups
EBA for PTSD	35.4% (135,160)	19.6% (74,792)	14.8% (56,300)	12.7% (48,320)	9.7% (37,163)	4.6% (17,684)
Fluoxetine	8.3% (31,528)	4.4% (16,797)	4.0% (15,392)	3.4% (13,103)	2.5% (9,607)	1.2% (4,419)
Paroxetine	4.9% (18,817)	2.4% (9,153)	2.1% (8,099)	1.8% (6,906)	1.4% (5,206)	0.7% (2,637)
Sertraline	20.6% (78,506)	10.8% (41,261)	7.2% (27,414)	6.1% (23,077)	4.8% (18,179)	2.2% (8,377)
Venlafaxine	6.0% (22,729)	2.8% (10,497)	1.9% (7,141)	1.7% (6,395)	1.3% (5,086)	0.7% (2,674)

Note. PTSD=Posttraumatic Stress Disorder; EBA=Evidence-Based Antidepressant

Table 4: VA Users Initiating Evidence-Based Antidepressants for PTSD with Adequate Duration from 2008-2013, by Receipt of Aligned PTSD Checklist Measurement

	Overall (52,907)	Category: With Aligned PCL Measurement (1,068)	Category: Without Aligned PCL Measurement (51,839)
Patient Characteristics			
Age, M (SD)**	45.3 (16.0)	37.8 (12.7)	45.4 (16.0)
Women, % (n)	8.3 (4,373)	9.4 (100)	8.2 (4,273)
Married, % (n)*	58.7 (31,072)	55.8 (596)	58.8 (30,476)
White Non-Hispanic, % (n)	66.4 (35,122)	65.5 (699)	66.4 (34,423)
OEF/OIF/OND Veteran, % (n)**	47.2 (24,968)	78.8 (841)	46.5 (24,127)
Rural, % (n)	35.7 (18,893)	33.8 (361)	35.8 (18,532)
Combat Exposure, % (n)	27.4 (14,510)	30.1 (321)	27.4 (14,189)
Sexual Trauma while in Military, % (n)	8.1 (4,285)	8.2 (88)	8.1 (4,197)
VA Disability Level 70% or Greater, % (n)**	60.0 (31,743)	66.9 (714)	59.9 (31,029)
Charleson Comorbidity Index 1 or greater, % (n)**	12.3 (6,501)	5.4 (58)	12.4 (6,443)
Psychotic Disorders, % (n)	3.4 (1,816)	3.5 (37)	3.4 (1,779)
Bipolar Mood Disorders, % (n)	4.3 (2,269)	3.5 (37)	4.3 (2,232)
Depressive Mood Disorders, % (n)**	69.2 (36,624)	77.5 (828)	69.1 (35,796)
Non-PTSD Anxiety Disorders, % (n)**	37.3 (19,726)	45.1 (482)	37.1 (19,244)
Traumatic Brain Injury, % (n)**	16.6 (8,769)	27.6 (295)	16.4 (8,474)
Alcohol Use Disorders, % (n)*	27.4 (14,490)	31.3 (334)	27.3 (14,156)
Opioid Use Disorders, % (n)*	2.8 (1,483)	4.0 (43)	2.8 (1,440)
Other Drug Use Disorders, % (n)	17.0 (8,993)	18.8 (201)	17.0 (8,792)
Service Use Characteristics			
Adequate Trial of EBP for PTSD, % (n)**	5.3 (2,798)	24.6 (263)	4.9 (2,535)
PTSD Outpatient Clinical Team Use, % (n)**	38.2 (20,189)	57.4 (613)	37.8 (19,576)
Outpatient Mental Health Visits, M(SD)**	15.0 (14.8)	22.9 (16.9)	14.9 (14.7)
Outpatient Substance Abuse Visits, M(SD)**	2.7 (11.2)	5.1 (16.0)	2.7 (11.1)
Outpatient Primary Care Visits, M(SD)*	3.5 (3.3)	3.3 (2.7)	3.5 (3.4)
ED Visit for Psychiatric Indication, % (n)	10.7 (5,677)	11.1 (118)	10.7 (5,559)
Acute Mental Health Inpatient Admission, % (n)*	8.2 (4,318)	9.9 (106)	8.1 (4,212)
Residential PTSD Admission, % (n)**	2.9 (1,518)	5.3 (57)	2.8 (1,461)
Residential Substance Abuse Admission**	2.2 (1,186)	4.2 (45)	2.2 (1,141)
Primary Prescribing Clinician Characteristics			
Age, M (SD)	51.9 (11.2)	51.8 (10.7)	51.9 (11.2)
Woman, % (n)	39.4 (20,847)	40.5 (433)	39.4 (20,414)
Physician, % (n)	76.3 (40,366)	75.8 (810)	76.3 (39,556)
Physician Assistant, % (n)	3.8 (2,004)	3.8 (41)	3.8 (1,963)
Nurse Practitioner, % (n)	19.1 (10,104)	19.3 (206)	19.1 (9,898)
Pharmacist, % (n)	0.7 (353)	0.8 (9)	0.7 (344)
Percentage of Time Seeing PTSD Patients in Various Settings	-	-	-
PTSD Service Section (PCT or residential), M (SD)**	14.1 (29.8)	20.1 (33.7)	14.0 (29.7)
Substance Abuse Service Section, M (SD)	2.0 (10.2)	2.5 (12.2)	2.0 (10.1)
Comorbid PTSD Substance Abuse Service Section, M (SD)	0.1 (1.7)	0.1 (1.9)	0.1 (1.7)
General Mental Health Service Section, M (SD)**	65.8 (40.3)	61.0 (40.9)	65.9 (40.3)
Integrated Care Service Section, M (SD)	6.5 (19.2)	5.6 (17.6)	6.6 (19.3)
Primary Care Service Section, M (SD)	7.7 (24.1)	7.3 (23.6)	7.7 (24.1)

Note. VA=United States Department of Veterans Affairs; PTSD=Posttraumatic Stress Disorder; M=mean, SD=standard deviation; OEF/OIF/OND=Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn, EBP=Evidence Based Psychotherapy; *p<0.05, **p<0.001

Table 5: Comparison of PTSD Symptomatic Outcomes for Patients who Initiated an EBA and Met Various Quality Standards, FY 2008-2013

Quality Standard	Patients with Measurement (n)	Baseline PCL, mean (SD)	Change in PCL		10-Point Drop plus LOD	
			Mean (SD)	Equivalence	% (n)	Equivalence
Comparisons of Unweighted Data (Covariates in Appendix 2)						
A) Adequate Duration	471	63.9 (9.5)	7.1 (12.6)	A=B, A=C, A=D, B=C, B=D, C=D	17.4 (82)	A=B, A=C, A=D, B=C, B=D, C=D
B) Adequate Duration and Dose plus/minus Refill	137	63.7 (10.0)	5.6 (12.2)		14.6 (20)	
C) Adequate Duration and Dose plus Refill and 1 Follow-Up	216	63.8 (10.1)	5.1 (13.1)		11.6 (25)	
D) Adequate Duration and Dose plus Refill and 3 Follow-Ups	244	65.7 (9.4)	5.6 (13.0)		13.9 (34)	
Comparisons of Weighted Data (Covariates in Appendix 3)						
A) Adequate Duration	471	64.1 (9.8)	7.0 (12.9)	A=B, A=C, A=D, B=C, B=D, C=D	17.3 (82)	A=B, A=C, A=D, B=C, B=D, C=D
B) Adequate Duration and Dose plus/minus Refill	137	64.3 (11.1)	6.3 (12.6)		15.7 (20)	
C) Adequate Duration and Dose plus Refill and 1 Follow-Up	216	64.4 (9.8)	5.4 (12.5)		10.7 (25)	
D) Adequate Duration and Dose plus Refill and 3 Follow-Ups	244	65.2 (10.8)	6.3 (15.5)		14.7 (34)	

Note. PTSD=Posttraumatic Stress Disorder, PCL=PTSD Checklist; LOD=Loss of PTSD Diagnosis; alpha for significant differences is $p<0.05/6 = 0.008$

Appendix 1: Antidepressant Medication Initiation in the Year Following Initial PTSD Diagnosis among Patients with No Antidepressant Prescriptions in the 2 Years Prior to Index PTSD Diagnosis, by Punitive Quality Standards

Fiscal Years	2004-2005	2006-2007	2008-2009	2010-2011	2012-2013	Overall
New PTSD Episodes, n	51,012	62,874	86,105	93,056	88,651	381,698
Number of ADs, M (SD)	1.8 (0.9)	1.8 (0.9)	1.8 (0.9)	1.8 (0.9)	1.8 (0.9)	1.8 (0.9)
Any Receipt						
Effective SSRI or SNRI	39.2% (19,979)	30.1% (18,914)	32.1% (27,629)	33.1% (30,816)	42.7% (37,822)	35.4% (135,160)
Fluoxetine	11.0% (5,612)	9.2% (5,789)	7.3% (6,276)	6.9% (6,429)	8.4% (7,422)	8.3% (31,528)
Paroxetine	7.2% (3,657)	5.7% (3,562)	4.3% (3,736)	3.9% (3,605)	4.8% (4,257)	4.9% (18,817)
Sertraline	20.1% (10,251)	13.1% (8,208)	18.8% (16,212)	20.4% (18,974)	28.0% (24,861)	20.6% (78,506)
Venlafaxine	5.5% (2,804)	5.4% (3,408)	5.1% (4,409)	5.8% (5,357)	7.6% (6,751)	6.0% (22,729)
Adequate Duration						
Effective SSRI or SNRI	22.7% (11,555)	16.4% (10,330)	17.4% (15,020)	17.7% (16,450)	24.2% (21,437)	19.6% (74,792)
Fluoxetine	6.3% (3,207)	5.0% (3,156)	3.8% (3,272)	3.5% (3,228)	4.4% (3,934)	4.4% (16,797)
Paroxetine	3.6% (1,841)	2.8% (1,752)	2.1% (1,817)	1.9% (1,734)	2.3% (2,009)	2.4% (9,153)
Sertraline	11.1% (5,649)	6.7% (4,211)	9.9% (8,525)	10.4% (9,631)	14.9% (13,245)	10.8% (41,261)
Venlafaxine	2.6% (1,316)	2.5% (1,576)	2.3% (1,956)	2.6% (2,395)	3.7% (3,254)	2.8% (10,497)
Adequate Dose and Duration						
Effective SSRI or SNRI	17.8% (9,074)	13.2% (8,265)	13.2% (11,357)	13.0% (12,120)	17.5% (15,484)	14.8% (56,300)
Fluoxetine	5.7% (2,907)	4.6% (2,898)	3.5% (3,028)	3.2% (2,949)	4.1% (3,610)	4.0% (15,392)
Paroxetine	3.3% (1,662)	2.5% (1,558)	1.9% (1,599)	1.7% (1,531)	2.0% (1,749)	2.1% (8,099)
Sertraline	7.7% (3,901)	4.7% (2,960)	6.7% (5,739)	6.8% (6,316)	9.6% (8,498)	7.2% (27,414)
Venlafaxine	1.7% (883)	1.8% (1,100)	1.6% (1,335)	1.8% (1,635)	2.5% (2,188)	1.9% (7,141)
Adequate Dose and Duration plus Refill						
Effective SSRI or SNRI	15.7% (8,028)	11.2% (7,070)	11.2% (9,632)	11.2% (10,421)	14.9% (13,169)	12.7% (48,320)
Fluoxetine	4.9% (2,491)	3.9% (2,418)	3.0% (2,568)	2.8% (2,565)	3.5% (3,061)	3.4% (13,103)
Paroxetine	2.9% (1,482)	2.1% (1,320)	1.6% (1,335)	1.4% (1,293)	1.7% (1,476)	1.8% (6,906)
Sertraline	6.7% (3,439)	4.0% (2,535)	5.5% (4,768)	5.7% (5,288)	8.0% (7,047)	6.1% (23,077)
Venlafaxine	1.6% (807)	1.5% (969)	1.4% (1,197)	1.6% (1,478)	2.2% (1,944)	1.7% (6,395)
Adequate Dose and Duration plus Refill and 1 Follow-Up						
Effective SSRI or SNRI	8.9% (4,534)	7.2% (4,538)	8.3% (7,184)	9.5% (8,877)	13.6% (12,030)	9.7% (37,163)
Fluoxetine	2.7% (1,368)	2.4% (1,509)	2.1% (1,838)	2.3% (2,116)	3.1% (2,776)	2.5% (9,607)
Paroxetine	1.7% (846)	1.4% (848)	1.2% (1,039)	1.2% (1,114)	1.5% (1,359)	1.4% (5,206)
Sertraline	3.8% (1,961)	2.6% (1,647)	4.2% (3,585)	4.9% (4,540)	7.3% (6,446)	4.8% (18,179)
Venlafaxine	0.9% (469)	1.0% (651)	1.1% (910)	1.4% (1,279)	2.0% (1,777)	1.3% (5,086)
Adequate Dose and Duration plus Refill and 3 Follow-Ups						
Effective SSRI or SNRI	4.4% (2,261)	3.7% (2,329)	4.3% (3,659)	4.5% (4,140)	6.0% (5,295)	4.6% (17,684)
Fluoxetine	1.3% (663)	1.2% (728)	1.1% (905)	1.0% (937)	1.3% (1,186)	1.2% (4,419)
Paroxetine	0.8% (418)	0.8% (492)	0.7% (566)	0.6% (551)	0.7% (610)	0.7% (2,637)
Sertraline	1.9% (971)	1.3% (809)	2.0% (1,754)	2.2% (2,064)	3.1% (2,779)	2.2% (8,377)
Venlafaxine	0.5% (254)	0.6% (362)	0.6% (539)	0.7% (665)	1.0% (854)	0.7% (2,674)

Note. PTSD=Posttraumatic Stress Disorder; AD=Antidepressant; M=Mean; SD=Standard Deviation

Appendix 2: Covariates for Comparisons of Quality Standards, 2008-2013 **(Unweighted)**

Patient Characteristics, N	A) Adequate Duration, n=471	B) Plus Adequate Dose +/- Refill, n=137	C) Plus Refill and 1 Follow-Up, n=216	D) Plus Refill and 3 Follow-ups, n=244	Pairwise Differences
Baseline PCL, M (SD)	63.9 (9.5)	63.7 (10.0)	63.8 (10.1)	65.7 (9.4)	No differences
Days Between Index PTSD diagnosis and Day 1 of AMT, M (SD)	60.1 (71.6)	72.5 (77.2)	73 (73.1)	50.5 (65.5)	B≠D
Days Between Baseline PCL and Day 1 of AMT, M (SD)	0.2 (7.0)	0.2 (6.6)	1.1 (6.8)	1.4 (7.1)	No differences
Days Between Follow-Up PCL and Day 84 of AMT, M (SD)	0.4 (8.4)	-0.1 (8.4)	-0.4 (8.0)	-1.2 (8.6)	No differences
Fiscal years 2008-2009, % (n)	5.1 (24)	5.1 (7)	3.2 (7)	4.1 (10)	No differences
Fiscal years 2010-2011, % (n)	34.4 (162)	40.1 (55)	31.5 (68)	34.4 (84)	No differences
Fiscal years 2012-2013, % (n)	60.5 (285)	54.7 (75)	65.3 (141)	61.5 (150)	No differences
Age, M (SD)	39.4 (13.8)	36.2 (12.6)	38.1 (12.3)	35.4 (10.1)	A≠D
Women, % (n)	10.6 (50)	2.9 (4)	8.3 (18)	11.5 (28)	A≠B, B≠D
Married, % (n)	55.8 (263)	62.8 (86)	60.6 (131)	47.5 (116)	B≠D, C≠D
White Non-Hispanic, % (n)	64.5 (304)	65.7 (90)	70.4 (152)	62.7 (153)	No differences
OEF/OIF/OND Veteran, % (n)	73.0 (344)	83.2 (114)	82.4 (178)	84.0 (205)	A≠C, A≠D
Rural, % (n)	34.0 (160)	38.7 (53)	38.9 (84)	26.2 (64)	C≠D
Combat Exposure, % (n)	29.3 (138)	26.3 (36)	28.2 (61)	35.2 (86)	No differences
Sexual Trauma while in Military, % (n)	8.7 (41)	5.1 (7)	6.5 (14)	10.7 (26)	No differences
VA Disability Level 70% or Greater, % (n)	63.1 (297)	63.5 (87)	71.3 (154)	72.1 (176)	No differences
Charleson Comorbidity Index 1 or greater, % (n)	6.8 (32)	4.4 (6)	6.5 (14)	2.5 (6)	No differences
Psychotic Disorders, % (n)	2.1 (10)	3.6 (5)	3.7 (8)	5.7 (14)	No differences
Bipolar Mood Disorders, % (n)	3.2 (15)	1.5 (2)	2.3 (5)	6.1 (15)	No differences
Depressive Mood Disorders, % (n)	75.8 (357)	78.1 (107)	76.9 (166)	81.1 (198)	No differences
Non-PTSD Anxiety Disorders, % (n)	45.6 (215)	44.5 (61)	48.1 (104)	41.8 (102)	No differences
Traumatic Brain Injury, % (n)	22.9 (108)	35.0 (48)	29.6 (64)	30.7 (75)	A≠B
Alcohol Use Disorders, % (n)	32.1 (151)	21.9 (30)	27.3 (59)	38.5 (94)	B≠D
Opioid Use Disorders, % (n)	2.8 (13)	4.4 (6)	3.7 (8)	6.6 (16)	No differences
Other Drug Use Disorders, % (n)	16.6 (78)	14.6 (20)	15.3 (33)	28.7 (70)	A≠D, B≠D, C≠D
Adequate Trial of Evidence-Based Psychotherapy for PTSD, % (n)	24.4 (115)	24.1 (33)	25.0 (54)	25.0 (61)	No differences
PTSD Outpatient Clinical Team Use (540 or 561), % (n)	58.8 (277)	52.6 (72)	53.2 (115)	61.1 (149)	No differences
Outpatient Mental Health Visits, M (SD)	28.2 (28.2)	25.7 (31.7)	24.4 (19.8)	40.2 (38.9)	A≠D, B≠D, C≠D
Outpatient Substance Abuse Visits, M (SD)	7.5 (31.2)	5.9 (28.7)	3.3 (9.7)	14.7 (42)	B≠D
Outpatient Primary Care Visits, M (SD)	3.4 (3.1)	3.5 (2.5)	3.4 (2.7)	3.8 (3.3)	No differences
Emergency Department Visit for Psychiatric Indication, % (n)	9.8 (46)	8.0 (11)	7.4 (16)	18.4 (45)	**A**≠D, B≠D, C≠D
Acute Mental Health Inpatient Admission, % (n)	7.2 (34)	5.8 (8)	6.9 (15)	20.1 (49)	A≠D, B≠D, C≠D
Residential PTSD Admission, % (n)	3.4 (16)	2.9 (4)	3.7 (8)	11.9 (29)	A≠D, B≠D, C≠D
Residential Substance Abuse Admission, % (n)	2.8 (13)	3.6 (5)	3.7 (8)	7.8 (19)	A≠D
Prescribing Clinician Characteristics, where known					
Age, M (SD)	51.7 (10.9)	54.0 (9.5)	52.8 (10.4)	49.9 (11)	C≠D
Women, % (n)	45.5 (178)	53.1 (60)	48.3 (85)	55.3 (110)	No differences
Physician, % (n)	71.3 (335)	78.1 (107)	80.6 (174)	79.5 (194)	No differences
Physician's Assistant, % (n)	5.1 (24)	3.6 (5)	3.2 (7)	2.0 (5)	No differences
Nurse Practitioner, % (n)	22.6 (106)	17.5 (24)	14.8 (32)	18.0 (44)	No differences
Pharmacist, % (n)	1.1 (5)	0.7 (1)	0.9 (2)	0.4 (1)	No differences
Percentage of time in PTSD Service, M (SD)	20.2 (33.5)	19.7 (33.9)	20.4 (35.1)	19.7 (33.0)	No differences
Percentage of time in Substance Abuse Service, M (SD)	2.5 (12.6)	2.6 (10.1)	2.3 (11.7)	2.9 (12.9)	No differences
Percentage of time in PTSD-Substance Abuse Service, M (SD)	0.0 (0.3)	0.0 (0.0)	0.0 (0.1)	0.3 (3.9)	No differences
Percentage of time in General Mental Health Service, M (SD)	58.8 (41.3)	60.9 (42.3)	65.5 (40.9)	61.3 (39.4)	No differences
Percentage of time in Integrated Care Service, M (SD)	6.7 (19.2)	3.6 (14.7)	3.5 (14.1)	6.3 (18.3)	No differences
Percentage of time in Primary Care Service, M (SD)	7.9 (24.3)	10.1 (28.1)	5.7 (21.1)	5.8 (21.1)	No differences

Appendix 3: Covariates for Comparisons of Quality Standards, 2008-2013 **(Weighted)**

Patient Characteristics, N	Adequate Duration, n=471	Plus Adequate Dose +/- Refill, n=137	Plus Refill and 1 Follow-Up, n=216	Plus Refill and 3 Follow-ups, n=244	Pairwise Differences
Baseline PCL, M (SD)	64.1 (9.8)	64.3 (11.1)	64.4 (9.8)	65.2 (10.8)	No differences
Days Between Index PTSD diagnosis and Day 1 of AMT, M (SD)	59.3 (72.1)	60.7 (67.1)	63.5 (67.8)	55.1 (86.7)	No differences
Days Between Baseline PCL and Day 1 of AMT, M (SD)	0.5 (7.0)	0.7 (6.6)	1.13 (7.0)	0.8 (7.4)	No differences
Days Between Follow-Up PCL and Day 84 of AMT, M (SD)	0.3 (8.5)	-0.7 (8.7)	0.0 (8.5)	-0.5 (9.0)	No differences
Fiscal years 2008-2009, % (n)	5.2 (24)	5.3 (7)	2.5 (7)	3.1 (10)	No differences
Fiscal years 2010-2011, % (n)	33.7 (162)	37.5 (55)	32.3 (68)	34.7 (84)	No differences
Fiscal years 2012-2013, % (n)	61.1 (285)	57.2 (75)	65.2 (141)	62.2 (150)	No differences
Age, M (SD)	38.2 (12.6)	36.3 (12.8)	37.8 (13.3)	36.8 (13.3)	No differences
Women, % (n)	11.0 (50)	4.7 (4)	**8.9 (18)**	11.3 (28)	No differences
Married, % (n)	55.2 (263)	59.3 (86)	56.5 (131)	51.2 (116)	No differences
White Non-Hispanic, % (n)	63.9 (304)	65.4 (90)	67.6 (152)	62.7 (153)	No differences
OEF/OIF/OND Veteran, % (n)	76.6 (344)	83.4 (114)	80.5 (178)	83.0 (205)	No differences
Rural, % (n)	33.8 (160)	35.9 (53)	37.0 (84)	26.6 (64)	No differences
Combat Exposure, % (n)	29.3 (138)	24.6 (36)	26.7 (61)	34.3 (86)	No differences
Sexual Trauma while in Military, % (n)	9.0 (41)	7.1 (7)	8.0 (14)	10.1 (26)	No differences
VA Disability Level 70% or Greater, % (n)	64.4 (297)	65.0 (87)	70.5 (154)	67.3 (176)	No differences
Charleson Comorbidity Index 1 or greater, % (n)	6.4 (32)	3.2 (6)	6.4 (14)	2.6 (6)	No differences
Psychotic Disorders, % (n)	2.2 (10)	3.2 (5)	3.3 (8)	4.1 (14)	No differences
Bipolar Mood Disorders, % (n)	3.3 (15)	1.4 (2)	2.2 (5)	4.3 (15)	No differences
Depressive Mood Disorders, % (n)	76.0 (357)	80.2 (107)	77.4 (166)	79.1 (198)	No differences
Non-PTSD Anxiety Disorders, % (n)	46.3 (215)	47.6 (61)	47.8 (104)	42.3 (102)	No differences
Traumatic Brain Injury, % (n)	24.6 (108)	30.9 (48)	29.9 (64)	28.1 (75)	No differences
Alcohol Use Disorders, % (n)	32.5 (151)	24.7 (30)	27.6 (59)	30.7 (94)	No differences
Opioid Use Disorders, % (n)	2.9 (13)	4.0 (6)	2.9 (8)	3.9 (16)	No differences
Other Drug Use Disorders, % (n)	17.0 (78)	13.6 (20)	15.5 (33)	21.8 (70)	No differences
Adequate Trial of Evidence-Based Psychotherapy for PTSD, % (n)	24.4 (115)	25.2 (33)	24.9 (54)	25.0 (61)	No differences
PTSD Outpatient Clinical Team Use (540 or 561), % (n)	58.9 (277)	58.7 (72)	53.2 (115)	58.0 (149)	No differences
Outpatient Mental Health Visits, M (SD)	28.8 (30.6)	25.7 (36.4)	25.6 (23.0)	31.7 (26.0)	No differences
Outpatient Substance Abuse Visits, M (SD)	7.6 (31.3)	6.0 (35.2)	3.0 (9.4)	9.0 (27.6)	A≠C
Outpatient Primary Care Visits, M (SD)	3.5 (3.3)	3.4 (2.7)	3.6 (3.2)	3.6 (3.4)	No differences
Emergency Department Visit for Psychiatric Indication, % (n)	10.0 (46)	8.4 (11)	8.1 (16)	12.5 (45)	No differences
Acute Mental Health Inpatient Admission, % (n)	7.9 (34)	5.3 (8)	6.8 (15)	12.2 (49)	No differences
Residential PTSD Admission, % (n)	3.7 (16)	2.2 (4)	3.7 (8)	6.8 (29)	No differences
Residential Substance Abuse Admission, % (n)	2.7 (13)	3.8 (5)	3.3 (8)	4.7 (19)	No differences
Prescribing Clinician Characteristics, where known					
Age, M (SD)	51.6 (12.2)	52.7 (12.7)	52.4 (10.9)	51.0 (12.6)	No differences
Women, % (n)	46.8 (178)	52.4 (60)	50.8 (85)	55.0 (110)	No differences
Physician, % (n)	74.2 (335)	79.0 (107)	78.6 (174)	79.3 (194)	No differences
Physician's Assistant, % (n)	4.7 (24)	4.0 (5)	3.8 (7)	1.7 (5)	No differences
Nurse Practitioner, % (n)	20.3 (106)	16.4 (24)	16.5 (32)	18.9 (44)	No differences
Pharmacist, % (n)	0.9 (5)	0.6 (1)	0.9 (2)	0.2 (1)	No differences
Percentage of time in PTSD Service, M (SD)	19.7 (33.7)	21.3 (39.3)	20.1 (35.7)	20.0 (37.0)	No differences
Percentage of time in Substance Abuse Service, M (SD)	2.6 (12.8)	1.6 (6.1)	2.5 (13.5)	2.3 (10.4)	No differences
Percentage of time in PTSD-Substance Abuse Service, M (SD)	0.0 (0.3)	0.0 (0.0)	0.0 (0.2)	0.3 (2.9)	No differences
Percentage of time in General Mental Health Service, M (SD)	61.4 (40.9)	63.8 (45.0)	62.2 (44.4)	61.6 (44.9)	No differences
Percentage of time in Integrated Care Service, M (SD)	5.8 (16.8)	3.1 (11.7)	4.9 (21.8)	6.0 (19.6)	No differences
Percentage of time in Primary Care Service, M (SD)	7.1 (22.6)	7.4 (22.8)	7.3 (30.1)	6.1 (24.6)	No differences