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14. ABSTRACT

We have achieved two main deliverables in Fiscal Year 2020. First, results of Aims 1-3 were published in The Journal of Clinical Psychiatry, explaining our methodology of extracting PTSD diagnoses and PCL measurements in VA users between 2016 and 2018. We also discussed clinical differences, including changes in PCL scores, among the five psychotropic medications assessed in this project (fluoxetine, sertraline, paroxetine, topiramate, and venlafaxine) .

Second, we re-built the study cohort to include all VA users with a PTSD diagnosis between October 1, 1999 and September 30, 2019. This new cohort will be used to complete Aim 4 of the project.

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 corporate data warehouse (CDW) 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.

In order to accomplish these aims, we needed to update and merge existing data and datasets from the VA. With this new cohort, we developed 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—50% completed
Task 4. Finalize study requirements, prepare for future funding, and dissemination of findings—25% completed

Our initial SOW called for the completion of Task 3 and part of Task 4 to be completed by the end of Year 3. Due to delay in obtaining the correct cohort, as described in the Major Activities section below, we requested and were granted a no-cost extension for one additional year (9/1/20-8/31/21). Progress on subtasks is described in detail below.

WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

Year 3 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.
   b. Determine whether each Veteran who received an AMT also received pre- and post-measurement with the PTSD Checklist (PCL).
   c. Determine whether each Veteran who received an AMT plus pre/post-measurement meets symptomatic criteria for PTSD by examining individual PCL items.
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.
   b. Create GEE models of PCL data to estimate change over time in overall symptoms and clusters of symptoms for patients included in the cohorts.
   c. Perform analyses of continuous and categorical change for the entire cohort to complete Aims 1-3.
   d. Perform analyses of continuous for each of 13 clinically important subgroups to complete Aim 4.
4. Finalize study requirements, prepare for future funding, and dissemination
   a. Complete final report and manuscript draft.
   b. Use final data to apply for future funding to continue work.
   c. Disseminate findings through national conferences and DoD presentations.

Major Activities

As previously reported, in Year 2 we discovered that the original cohort provided to us by the VA Informatics and Computing Infrastructure (VINCI) only included VA users with a diagnosis of PTSD between FY 2016 and FY 2018. While this smaller cohort was sufficient for the completion of **Aims 1-3** (acute phase change in overall PTSD symptoms, follow-up phase acute psychiatric care use, and acute phase change in PTSD symptom clusters), it was not large enough for the completion of **Aim 4** (acute phase change in overall PTSD symptoms for clinically important subgroups). Therefore, **in Year 3 we used the smaller FY 2016-2018 cohort to complete Aims 1-3 while at the same time rebuilding a larger cohort include VA users with a diagnosis of PTSD between FY 1999 and FY 2019 in order to complete Aim 4 subgroup analyses**. As a result, we have fully completed **Task 2** and have made significant progress towards **Tasks 3 and 4.**

Our manuscript describing the results of Aims 1-3 has been accepted for publication at the *Journal of Clinical Psychiatry* and is described below under

Significant Results and Products. Notably, as our pilot analyses were previously published at the *Journal of Clinical Psychiatry* during Year 2, we now have two papers from the current award published in this prestigious journal. Additionally, during year 3 we published two methods papers regarding our use of medication and psychotherapy variables for causal analyses in *Administration and Policy in Mental Health and Mental Health Services Research*. These are also described below under Products. As we also published a methods paper during year 2, we now have five total papers from the current award.

Significant Results

With the smaller cohort, including VA users with a clinical diagnosis of PTSD between FY 2016 and 2018, we showed that when using the version of the PTSD Checklist (PCL) aligned to the current case definition for PTSD (the PCL-5, which reflects the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition, or DSM-5), venlafaxine is associated with superior acute-phase remission rates compared to fluoxetine, sertraline, paroxetine and topiramate. It appears that this could be driven by venlafaxine's superior effectiveness in the negative alterations in cognitions and mood symptom cluster, which was added to the diagnosis of PTSD in DSM-5. Additionally, medication continuation during the 6-month follow-up phase was protective against acute psychiatric care use regardless of the agent chosen. These results, summarizing **Aims 1 – 3**, were accepted for publication at the *Journal of Clinical Psychiatry*.

As shown in Table 1 below, we have repeated **Task 2** with the updated and expanded cohort, which includes all VA users with a diagnosis of PTSD between FY 1999 and FY 2019. Within this group, we have identified adequate medication trials (AMTs) meeting all inclusion and exclusion criteria for Aim 4 analyses (Table 1). This work involved mining PCL data from both structured fields in the VA Corporate Data Warehouse (CDW) and unstructured clinical notes, and then aligning those measurements with prescription data. We captured PCL data from clinical notes using a natural language processing (NLP) algorithm developed in another DoD-funded effort (JW140056, PI: Maguen). We also applied NLP algorithms to the same notes to detect use of evidence-based psychotherapy, an important explanatory covariate for our work. After identifying all available PCL scores, we used a crosswalk developed by the National Center for PTSD to convert scores from symptomatic assessments using the previous version of the PCL (PCL-IV) to PCL-5 scoring. This allowed us to apply the PCL-5 diagnostic cutoff of 31 across versions of the PCL. Thus, all patients to be included in our Aim 4 analysis have a severity score that is consistent with a diagnosis of PTSD near the initial medication fill (baseline) and have a follow-up PCL score near the 12-week point (follow-up).

Table 1: Adequate Medication Trials with Pre/Post PTSD Checklist (PCL) Data Availability*

Population	Agent					Total
	Fluoxetine	Sertraline	Paroxetine	Topiramate	Venlafaxine	
Overall	2,419	2,690	989	666	1,228	7,992
Women	365	272	104	138	183	1,062
White Non-Hispanic	1,585	1,702	669	423	872	5,251
Black Non-Hispanic	391	471	159	118	152	1,291
Hispanic	275	308	105	83	124	895
Post-9/11 Veteran	1,693	1,869	715	516	857	5,650
Vietnam Veteran	158	181	67	19	78	503
Combat	1,532	1,664	650	475	786	5,107
Military Sexual Trauma	333	286	105	117	170	1,011
Pain Disorder	1,471	1,618	604	483	847	5,023
Headache Disorder	543	552	220	379	353	2,047
Psychotic Disorder	50	73	17	10	44	194
Bipolar Disorder	102	104	55	71	54	386

Depressive Disorder	1,727	1,871	673	462	947	5,680
Anxiety Disorder	747	850	337	213	427	2,574
Traumatic Brain Injury	199	278	105	119	183	884
Alcohol Use Disorder	680	757	227	180	365	2,259
Opioid Use Disorder	125	138	41	36	71	411
Other Substance Disorder	370	466	165	99	200	1,300

Note. *Patients were selected for this cohort based on having a VHA PTSD diagnosis between October 1, 1999 and September 30, 2019. All PCL scores were scaled to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) scoring, including baseline PCL within one month before or two weeks after the first prescription, and follow-up PCL within 2 weeks before or one month after the 12-week mark.

Overall, there were a total of 7,992 AMTs involving both baseline and follow-up PCL measurement. This includes 2,491 AMTs of fluoxetine, 2,690 of sertraline, 989 of paroxetine, 666 of topiramate, and 1,228 of venlafaxine. For Aim 4 subgroup analyses, we will have adequate power to detect small between-group differences in effect for most comparisons (minimum cell size 288), although in some cases (e.g., paroxetine in women) we may be limited to detecting medium between group differences (minimum cells size 104), and in others (e.g., venlafaxine in bipolar disorder) we may be limited to detecting large differences (minimum cell size of 41). In just a few cases (topiramate in Vietnam Veterans, paroxetine and topiramate in patients with comorbid psychotic disorders, topiramate in patients with comorbid opioid use disorders), we will not have meaningful power to detect between-group differences.

Other Achievements

We have submitted a proposal to the Peer Reviewed Medical Research Program (PRMRP) in response to their call for Expansion Award applications. This project, entitled "Clinical Effectiveness of Long-Acting Injectable Naltrexone for Posttraumatic Stress Disorder and Alcohol Use Disorder", would build off our current PTSD cohort in order to assess the effectiveness of medications for Alcohol Use Disorder (AUD) in patients with comorbid AUD and PTSD. We will further improve the methodologies developed for this current project in order to expand upon current knowledge of treatments for PTSD and AUD.

Additionally, our proposal entitled "Identification of Novel Agents to Treat PTSD using Clinical Data" was selected for funding as an R-01 award from the National Institute of Mental Health. This project, which officially started in May 2020, uses a statistical method called Tree Scan to identify non-psychotropic medications that are associated with PTSD symptom improvement. Already, we have developed a phylogenic tree of FDA-approved medications classified by mechanism. At this time, we are both setting up Tree Scan software in a special VINCI development workspace and building files to scan for non-psychotropic medications with potential PTSD effectiveness using the PCL files described above.

Goals Not Met

We have not yet finalized our larger analytic dataset for **Aim 4**. As previously discussed, we have requested and received approval for a no-cost extension in response to us needing to re-develop the cohort in Year 2. By the second quarter of Year 4, we anticipate finalizing analytic datasets for the completion of subgroup analyses (**Task 3**). Results will be disseminated through presentations at scientific conferences and manuscript publication (**Task 4**).

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

The primary professional development from this award has involved collaborations developed to pursue additional research funding using the cohort developed for this award. For the newly funded NIMH R01, Dr. Shiner partnered with an Multiple Principal Investigator, epidemiologist Dr. Jaimie Gradus, to learn additional data mining techniques including tree scan. For the PRMRP expansion award proposal, Dr. Shiner partnered with Dr. Gradus' colleague, epidemiologist Dr. Elanor Murray, to propose cutting edge techniques that frame retrospective comparative effectiveness analyses as the observational emulates of prospective randomized trials. This framework allows for additional analyses to control against bias due to loss to follow-up and non-completion of the intervention. Dr. Shiner has continued to work with psychologist Dr. Shira Maguen and informaticist Dr. Olga Patterson to leverage NLP products from a previous award (JW140056, PI: Maguen) to improve the quality of work performed in the current DoD award. Dr. Shiner has also been invited to work with Dr. Maguen's colleague, psychiatrist Dr. Thomas Neylan, to participate in the drug selection subgroup for DoD adaptive platform trials of medications for PTSD. Finally, VERANNE is in the late stages of talks with Otsuka and Lundbeck to fund Dr. Shiner's VA research team to examine the comparative safety and effectiveness of atypical antipsychotic augmentation of FDA-approved medications for PTSD using VA data (note: Dr. Shiner would not directly receive any funds from Pharma). A framework to evaluate the safety and effectiveness of atypical antipsychotics in Veterans with PTSD will become critical if the Otsuka product, Brexpiprazole (currently in phase III trials), is eventually approved for use in PTSD.

In sum, these collaborations have allowed us to leverage the current DoD award into multiple awards and proposals. This has both increased the impact of our work and will make us competitive if the DoD releases an RFP for center grants in psychopharamcoepidemiology.

HOW WERE THE RESULTS DISSEMINATED TO COMMUNITIES OF INTEREST?

As described in Significant Results above, a manuscript was published summarizing preliminary results of **Aims 1 – 3**. Dr. Shiner was also scheduled to present these results in August 2020 at the Military Health Research Consortium Annual Meeting in Kissimmee FL, but the conference was canceled due to the COVID-19 pandemic. Dr. Shiner did present on this general line of work, including work specifically related to this DoD award, at six meetings over the last year. These presentations are described in Products, below.

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

During year 4, we plan to finalize our dataset and complete all Aim 4 subgroup analyses. Additionally, we plan to prepare one additional manuscript describing Aim 4 results, one additional methods paper describing the development of our PCL database, and one additional methods paper describing availability of evidence-based psychotherapy data in the 20-year longitudinal cohort developed for this award. As we have travel funds remaining from the cancellation of Military Health Research Consortium Annual Meeting, we will apply to present our work again next year.

IMPACT

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

The publication resulting from work done in Years 2 and 3 has highlighted small differences in effectiveness of the five psychotropic medications primarily prescribed for PTSD. The results presented in this paper support that venlafaxine may have superior effects on acute remission of PTSD. Although more study is needed, these results may impact prescribing patterns within the VA for patients with PTSD.

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
Year 3 work was completed as anticipated. After our initial difficulty obtaining the correct cohort, the rebuild progressed smoothly and all anticipated summaries and analyses were completed as expected.

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

Nothing to report.

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: Aims 1-3

Shiner, B., Leonard, C.E., Gui, J., Schnurr, P.P., Hoyt, J.E., Young-Xu, Y., Watts, B.V. (2020) Comparing Medications for DSM-5 PTSD in Routine VA Practice, Journal of Clinical Psychiatry (In Press).

Journal Publications: Methods

Shiner, B., Leonard Westgate, C., Gui, J., Cornelius, S., Gradus, J.L., Schnurr, P.P., Watts, B.V. (2020) 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, (Online First: doi: 10.1007/s10488-020-01047-w).

Shiner, B., Leonard Westgate, C., Gui, J., Cornelius, S., Maguen, S., Watts, B.V., Schnurr, P.P. (2020) Measurement Strategies for Evidence-Based Psychotherapy for Posttraumatic Stress Disorder Delivery: Trends and Associations with Patient-Reported Outcomes, Administration and Policy in Mental Health and Mental Health Services Research, 47(3): 451-67.

Conference Presentations: Posters

08/2020 – "Comparing Medications for DSM-5 PTSD in Routine VA Practice." Military Health Research Consortium Annual Meeting, Kissimmee FL (Conference canceled due to COVID-19 Pandemic).

Conference Presentations: Talks

04/2020 – "Transforming the Practice of Mental Health Care: The Big Picture (Symposium Member)." NIMH Division of Translational Research, Bethesda MD (Virtual due to COVID-19 Pandemic).

04/2019 – "Use of Antidepressants to Treat PTSD." VA Psychotropic Drug Safety Initiative, West Haven CT (Virtual due to COVID-19 Pandemic).

12/2019 – "Measurement Strategies for Evidence-Based Treatments for PTSD: Trends and Associations with Patient-Reported Outcomes." Dartmouth Medical School Grand Rounds, Lebanon NH

12/2019 – "Measurement Strategies for Evidence-Based Psychotherapy for PTSD: Trends and Associations with Patient-Reported Outcomes." International Society for Traumatic Stress Studies Annual Meeting, Boston MA

10/2019 - "Measurement Strategies for Evidence-Based Psychotherapy for PTSD: Trends and Associations with Patient-Reported Outcomes." VA Health Services Research and Development Annual Meeting, Washington DC

09/2019 – "Tracking Use of VA-Recommended Treatments for PTSD." Mental Health Service Grand Rounds, VA Medical Center, White River Junction VT

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

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.
Sarah Cornelius, BS (Research Coordinator): No change.

Name:	Luke Rozema
Project Role:	Programmer
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	6.0
Contribution to Project:	Mr. Rozema cleaned data for the study cohort, prepared data for the annual report, and prepared pilot data for the Expansion Award proposal.
Funding Support:	Congressionally Directed Medical Research Program

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

As described above, Dr. Brian Shiner has received funding from the National Institute of Mental Health (NIMH) to conduct additional analyses on the cohort developed for this project. The effort for this project is counted under his position at his academic affiliate, Dartmouth-Hitchcock Clinic. Under this effort, he can continue with both the new NIMH award and the current DoD award.

WHAT OTHER ORGANIZATIONS WERE INVOLVED AS PARTNERS?

For Year 3, we have begun Joint Personnel Agreements with our academic affiliate (Dartmouth-Hitchcock Clinic) for Drs. Shiner, Watts, and Schnurr. This allows study funds to be used for salary support.

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 three manuscripts published thus far, as mentioned in **PRODUCTS** above.

Text Word Count: 2,998; Abstract Word Count: 249; Tables: 4; Supplementary Tables: 2

Comparing Medications for DSM-5 PTSD in Routine VA Practice

Running Title: Medications for DSM-5 PTSD

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Previous Presentations: None

Disclosures and acknowledgements: The authors report no conflicts of interest.

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ABSTRACT

Objective: Fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine have previously shown efficacy for PTSD. One prior study using VA medical records data to compare these agents found no differences in symptom reduction in clinical practice. We address several weaknesses in that study, including limited standardization of treatment duration, inability to account for prior treatment receipt, use of an outdated symptomatic assessment for PTSD, and lack of functional outcome.

Method: We identified 834 VA outpatients with DSM-5 clinical diagnoses of PTSD between October 2016 and March 2018 who initiated one of the medications and met pre-specified

criteria for treatment duration and dose, combined with baseline and endpoint PTSD checklist-5 (PCL-5) measurements. We compared 12-week acute phase changes in PCL score and remission of PTSD symptoms. We compared use of acute psychiatric services use in the subsequent 6-month continuation phase.

Results: In the acute phase, patients improved by a mean of 6.8-10.1 points on the PCL-5 and 0.0%-10.9% achieved remission of PTSD symptoms. Those taking venlafaxine were significantly more likely to achieve remission ($p<0.0001$). In the continuation phase, there were no differences in acute psychiatric care use between medications. Those who continued their medication were less likely to use acute psychiatric services (HR=0.55; $p=0.03$).

Conclusion: There may be an advantage to venlafaxine over other agents in achieving acute-phase remission for DSM-5 PTSD routine clinical practice, but this requires further study. Regardless of the agent chosen, medication cessation during the continuation phase is associated with a higher risk of acute psychiatric care use.

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, avoidance of trauma reminders, negative alterations in cognitions and mood, and increased arousal and reactivity.[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]

Randomized controlled trials (RCTs) show that effective treatments for PTSD include both pharmacologic and psychotherapeutic approaches.[4,5] Several individual medications have shown efficacy as PTSD treatments in placebo-controlled RCTs.[4,5] Because there is limited data comparing medications that are individually superior to placebo to one another in a single population, one prior VA study used electronic medical record (EMR) data from 2008-2013 to compare the real-world clinical effectiveness of five efficacious medications.[6] While that study found no differences in symptom reduction between fluoxetine, sertraline, paroxetine, topiramate, and venlafaxine, there were several weaknesses. These included limited standardization of treatment duration, inability to account for prior treatment receipt, use of an outdated patient-reported outcome measure (PROM) for PTSD that aligned with the fourth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV),[7] and lack of a functional outcome. We sought to improve upon this study by addressing these limitations.

Therefore, we conducted a retrospective comparative effectiveness study of the same five medications for PTSD using contemporary VA EMR data. We accounted for prior receipt of evidence-based pharmacologic and psychotherapeutic approaches for PTSD dating back almost 20 years, standardized acute-phase treatment duration at 12 weeks, and aligned acute-phase treatment with administration of the PROM for PTSD that is updated for the fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[1] Additionally, we compared the functional outcome of acute psychiatric services use in the subsequent 6-month continuation phase among the five agents. This replication and extension is important both to ensure that the prior null finding is not due to type II error and because different treatments may be effective under the DSM-5 case

conceptualization of PTSD,[8-10] which was implemented in 2013 and has an increased emphasis on negative alterations in cognitions and mood compared to DSM-IV.[1,7]

Method

Data Sources

This was a retrospective chart review. We used the VA Corporate Data Warehouse (CDW) to identify all VA users with a DSM-5 clinical diagnosis of PTSD (F43.1x) from 10/1/2016-3/7/2018. While DSM-5 was published in 2013, development and EMR-based implementation of related diagnostic and outcomes assessment tools in the VA occurred slowly, thus we chose 10/1/16 as the start date. We obtained information on services use, clinical diagnoses, pharmacy data, and standardized PTSD symptom measures from the CDW for these patients. This study was approved by the Veterans Institutional Review Board of Northern New England.

Cohort Selection

We identified patients who initiated a course of fluoxetine, sertraline, paroxetine, topiramate, or venlafaxine. The study sample was further restricted to those who met our criteria for adequate acute phase medication management. Patients receiving continuous treatment of sertraline, fluoxetine, paroxetine, venlafaxine, or topiramate daily for ≥12 weeks at an adequate dose were considered to have received an adequate medication trial (AMT). Adequate doses, which were required for the final 8 weeks only to allow for titration, were as follows: fluoxetine ≥20 mg, paroxetine ≥20 mg, sertraline ≥100 mg, topiramate ≥100 mg, and venlafaxine ≥150 mg.

For our outcomes analysis, we further restricted to those who received baseline PTSD symptom measurement within 2 weeks of treatment initiation, as well as follow-up symptom measurement within 2 weeks of the 12-week point, and met our symptomatic criteria for PTSD at baseline (defined below).

PTSD Symptoms

We measured PTSD symptoms using the DSM-5 PTSD Checklist (PCL-5),[11] which is administered in routine VA clinical practice. We used a baseline cutoff score of ≥31 out of 80 due to optimal efficiency for diagnosing PTSD in Veterans, compared to the gold-standard Clinician Administered PTSD Scale for DSM-5.[12] Our minimal symptomatic criteria required a score of "moderate" or higher on one avoidance symptom, two negative alterations symptoms, and two increased arousal symptoms.

While a threshold for clinically meaningful change had not yet been established when we implemented our coding rules, the largest prospective trial using the PCL-5 at that time used a severity score of ≤18 as a cutoff for remission.[13] Therefore, we considered a score of ≤18 plus no longer meeting symptomatic criteria to be consistent with remission at follow-up. 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.

Acute Psychiatric Services Use

We determined whether patients were admitted to a VA psychiatry unit (acute inpatient or observation) or visited a VA emergency room for a primary psychiatric indication during the six-month continuation phase, which followed the initial 12-week acute phase.

Independent Variables

We measured six groups of covariates that could plausibly affect the relationship between treatment and outcome. See Table 1 for details.

Analysis

To understand how AMTs with aligned PCL measurement differed from AMTs initiated without aligned PCL measurement from 10/1/2016-3/7/2018, we compared covariates describing concurrent treatment, primary prescribing clinicians, patient characteristics, VA service use characteristics, and comorbidities using χ^2 analysis and t-tests, as appropriate.

To account for differences in covariate profile among trials of each of the five medications, we used the RAND Toolkit for Weighting and Analysis of Nonequivalent Groups (TWANG).[15] 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 trial would be of each medication.[16] We estimated propensity scores with multinomial logistic regression using generalized booster effects,[17] in which the dependent variable is an indicator for each of the five medications and the independent variables are an anti-parsimonious specification of variables that have a plausible correlation with the outcome (i.e. our six groups of covariates).[16,17] Using these propensity scores, we weighted participants in order to balance the covariate distributions across medications.

We compared continuous and categorical outcomes among the five groups with regression analyses, using 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. These weighted groups were defined by the inverse of the propensity scores and adjusted covariates unbalanced at the $p<0.01$ level after TWANG weighting. In balancing over 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. For acute-phase continuous outcomes of pre/post change in total PCL score and sub-scores, 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 from baseline to follow-up. For our categorical outcome of remission, 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 remission. We assessed the potential contribution of unmeasured confounding on significant baseline to follow-up 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.[18,19]

Finally, for the continuation phase we used a weighted proportional hazard models to measure differences in acute psychiatric services use in the subsequent 6-month continuation phase, controlling for symptom change during the acute phase as well as whether there was prescription fill evidence that patients continued to take each medication. 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,[15] and models to detect unmeasured confounding using the R EVALUE package.[20]

Results

There were 834 AMTs aligned with PCL measurement and 38,089 AMTs that were not aligned with PCL measurement. Patients who had AMTs aligned with PCL measurement generally contributed only one trial (Table 2), had received few adequate prior trials of evidence-based treatments for PTSD, and had severe baseline PTSD symptoms (M=57.8; SD=11.1). Inclusion of data from the early implementation of the EMR-based PCL-5 tool (10/1/2014-9/30/2016) would have yielded a maximum of 21 additional AMTs aligned with PCL measurement while making the analytic cohort less representative of the overall population receiving AMTs during the period of examination. There were 16 cases where AMTs aligned with PCL measurement overlapped, and all of these cases involved concurrent prescribing of topiramate with one of the four antidepressants. AMTs associated with PCL measurement in our analytic cohort differed from contemporaneous AMTs without PCL measurement in many ways (Table 3). Most notably, AMTs with measurement coincided with higher levels of all forms of individual and group psychotherapy, including PE, CPT-I, and CPT-G.

The number of participants in the analytic cohort receiving each medication ranged from 307 who received sertraline to 87 who received paroxetine. While there were differences among the medication treatment groups (Supplementary Table 1), our weighting procedure allowed us to balance almost all covariates (Supplementary Table 2). The exceptions were the percentage of time the primary prescribing clinician spent

working in the integrated care service section and the percentage of Vietnam veterans receiving each medication, with both being significantly lower in the topiramate group. Therefore, these variables were retained as covariates, along with a covariate for concurrent antidepressant and topiramate prescribing, in subsequent analyses. PTSD symptom measurement was well-aligned to acute-phase medication treatment, with participants' baseline PCLs administered at 1.1 days (SD=6.4) days after the start of the medication and end-point PCLs were administered at 80.8 days (SD=10.3) later. Mean baseline PCL scores indicated a high burden of symptoms, ranging tightly from 57.5 (SD=10.9) for the sertraline group to 58.6 (SD=11.8) for the venlafaxine group.

All five of the medications were associated with moderate acute phase improvements in PTSD symptoms (Table 4). The mean improvement in total PCL score ranged from 6.8 points for the paroxetine and topiramate groups to 10.1 points for the venlafaxine group; acute phase remission rates ranged from 0% for the paroxetine group to 10.9% for the venlafaxine group. While there was no difference in total PCL change between the agents, there was a significant overall difference in achievement of remission ($p<0.0001$). Pairwise comparisons indicated superior achievement of remission between the venlafaxine group compared to other groups (venlafaxine versus fluoxetine $p=0.008$, venlafaxine versus paroxetine, sertraline, and topiramate $p<0.0001$). We could not calculate E-values for comparisons involving paroxetine as there were no remissions in the paroxetine group. However, where they could be calculated, E-values indicated the superior achievement in acute phase for the venlafaxine group to be robust (venlafaxine versus fluoxetine 7.3, versus sertraline 4.2, versus topiramate 15.2). Similarly, pairwise comparisons indicated inferior achievement of remission for paroxetine compared to all

other groups ($p<0.0001$). Finally, sertraline was significantly superior to topiramate in achievement of acute phase remission ($p<0.0001$; E=6.0).

There was a very limited range of change in PTSD symptom clusters and sleep item scores, with the greatest differences being between change in negative alterations in cognitions and mood for the venlafaxine group versus the other groups (-4.2 for venlafaxine versus -2.2 to -2.8 for the other groups). However, these differences were not statistically significant.

In our weighted survival analysis examining acute psychiatric care use in the six-month continuation phase, there were 57 events. We added a time-varying co-variate for whether patients stayed on their medication in the continuation phase and controlled for change in total PCL during the acute phase in addition to the unbalanced covariates. While we found no difference between medications in acute psychiatric care use during the continuation phase, there was a significant protective effect for medication adherence (HR=0.55; $p=0.03$).

Discussion

We compared the effectiveness of five evidence-based medications for DSM-5 PTSD and found that they all appear to be effective in routine clinical practice. Furthermore, we found evidence of possible superiority of venlafaxine in achieving acute phase remission. Though there were no between-groups differences in the continuation phase, our findings indicate that medication continuation beyond the initial 12 weeks of treatment is associated with lower risk of acute psychiatric care use such as psychiatric admission. This finding, combined with our finding that patients in all groups experienced a modest level of symptomatic improvement during the acute phase, even after controlling for other

important patient and concurrent treatment factors, supports our assertion that these five agents are effective in clinical practice. Our findings are consistent with meta-analytic findings that have suggested that fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine are efficacious treatments for PTSD in RCTs.[4,5]

We believe this study achieved our goal of improving upon the prior VA study comparing these five agents in routine practice,[6] and these changes may have accounted for the differences in findings. Firstly, we achieved far better standardization of treatment duration. While there was a wide range of time between baseline and follow-up symptomatic measurements in the prior VA study (mean length of 254.1 days; SD=119.5 days), we standardized the trial length and achieved a treatment duration that better approximated the typical acute phase clinical trial (mean length of 80.8 days; SD=10.3 days). Thus, we have significantly decreased the heterogeneity of exposure and improved the comparability of our retrospective results with those of prospective studies. Standardizing the acute phase treatment period also allowed us to add a continuation phase and related functional outcome (acute psychiatric services use). Second, we have accounted for prior evidence-based PTSD treatment receipt, including both psychotherapy and medication. We found that 19.0% of patients had previously received an adequate evidence-based medication trial and 6.8% had previously received an adequate evidence-based psychotherapy trial. Measuring this allowed us to account for differing levels of treatment resistance, as patients in the paroxetine, topiramate, and venlafaxine groups were more likely to have received prior adequate evidence-based medication trials. Third, this study used the PCL-5. The PCL-5 represents the current case conceptualization of PTSD. Importantly in this version, the avoidance and numbing items were split into

separate clusters, and additional items have been added to the prior numbing items to make the new negative alterations in cognitions and mood cluster. While the finding was not statistically significant, it was notable that patients in the venlafaxine group had the greatest magnitude of change in the negative alterations in cognitions and mood cluster. These symptoms were emphasized in the transition between DSM-IV and DSM-5 definitions of PTSD. Thus, better standardization of treatment duration, an ability to account for prior treatment resistance, and changes in the PTSD case definition may have all contributed to our finding of possible acute phase superiority for venlafaxine over other agents.

While we found that all the medication treatments for PTSD that we studied were effective in clinical practice, their effect seemed somewhat 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, Rauch et al.'s recent four-site VA and private sector study of PTSD treatment approaches for Iraq and Afghanistan Veterans included a sertraline plus enhanced medication management arm.[21] Enhanced medication management consisted of eight manualized 30-minute appointments over the first 12 weeks for those randomized to sertraline.[22] Sessions included psychoeducation and support from prescribing clinicians. Participants experienced a decrease PTSD symptom severity from 56.2 to 42.8 on the version of the PCL corresponding to DSM-IV over the first 12 weeks. This translates to an approximately 15-point improvement on the PCL-5,[23] and compares to a 7.5-point PCL-5 improvement in our sertraline group. The reasons for possible reduction in effectiveness are unknown. One possibility is that that enhanced medication management practices are

uncommon in routine practice, but as in psychotherapy, manualization may be required to obtain maximum benefit from psychopharmacologic approaches to treat PTSD.

There are several major limitations to our study, all of which are inherent to our uncontrolled, retrospective cohort design. First, participants meeting PCL-based inclusion criteria for our analytic cohort differed significantly from those receiving adequate medication trials without PCL measurement in several ways. Most notably, those with aligned PCL measurement received far more psychotherapy. The limited availability of PCL data indicates low use of measurement-based care (MBC) in routine psychopharmacology practice, despite a VA initiative to promote MBC starting in 2016.[24] Low use of MBC indicates an emerging quality problem,[25] as proactive measurement-driven approaches to psychotropic prescribing are associated with superior clinical outcomes.[26] Moreover, we have no clear understanding of whether these findings would apply to non-veterans with PTSD. Second, we 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, while patients could have met our prescribing standard with a single 90-day initial supply, 77.3% of patients finished their initial supply and requested refills. Lastly, we only considered PTSD outcomes and acute psychiatric care use, with PTSD outcomes based on a self-report measure. Depression and quality of life measures were not available, but they may have enriched our exclusive focus on PTSD outcomes.

We conclude that there may be an advantage to venlafaxine over other established medications in achieving acute-phase remission for DSM-5 PTSD routine clinical practice. However, additional prospective research is needed to confirm this result. Regardless of

the agent chosen, medication cessation during the continuation phase is associated with a higher risk of acute psychiatric care use. Our study lacks adequate sample size to adequately address issues regarding either specific medication effects on specific symptoms or patient characteristics that predict response with a particular medication. These are both fertile areas for future research.

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 appears that venlafaxine may have superior effects in helping patients achieve acute phase (12-week) remission, but this requires further study.

-Regardless of which agent is used, medication adherence in the continuation phase (subsequent 6 months) is associated with superior functioning, as indicated by less use of acute psychiatric services.

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, 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 during the 12-week acute treatment phase and improved functioning in the 6-month continuation phase. Patients in the venlafaxine group were more likely to experience remission of their PTSD symptoms during the acute phase, compared to patients in the other treatment groups. However, the possible superiority of venlafaxine over other established medications in achieving acute-phase remission for DSM-5 PTSD should be evaluated with additional prospective research.

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TABLES & APPENDICIES

Table 1: Explanation of covariates	
Trial Characteristics	
Number of Adequate Medication Trials (AMTs) Aligned with PTSD Checklist (PCL) Measurement	Adequate trials of fluoxetine, paroxetine, sertraline, topiramate, or venlafaxine aligned with PCL measurement that each patient contributed to the outcomes analysis. Trials of different agents could overlap or dovetail, but we required a one-year gap in prescriptions to count as a new trial of the same agent.
PCL Severity and Timing	Baseline PCL score, number of days between first available PTSD diagnosis and baseline PCL, number of days from baseline PCL to follow-up PCL for each trial included in the outcomes analysis.
Number of Prior AMTs	AMTs with or without PCL measurement between 1999 and the start of each trial included in the outcomes analysis.
Number of Prior Adequate Prolonged Exposure (PE) or Cognitive Processing Therapy (CPT) Trials[a]	Episodes where patients received ≥8 sessions PE or CPT over the course of one year between 1999 and the start of each medication trial included in the outcomes analysis.
Concurrent Treatments	Additional treatments received at the same time as an AMT associated with PCL measurement
Psychotherapy	Categorical receipt and number of sessions
PE[a]	Individual only
CPT[a]	Group and individual
Other psychotherapy	Group and individual
Medications	Categorical receipt of other antidepressants, sedative hypnotics, opioids, atypical antipsychotics, prazosin, medications for alcohol abuse including naltrexone or acamprosate, and opioid replacement medications including buprenorphine or methadone prescribed within the context of methadone treatment clinic
Primary Prescribing Clinician Characteristics	Clinician who wrote the plurality of each patient's psychotropic prescriptions during the 12-week treatment period
Age	Continuous
Gender	Categorical male or female
Professional background	e.g. psychiatrist or nurse practitioner
Percent of time spent seeing PTSD patients in various settings	e.g. specialized PTSD clinic or primary care clinic, based on 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.
Baseline Patient Characteristics	Demographics, military service characteristics
VA Health Service use Characteristics	Assessed in the year preceding baseline PCL.
Outpatient visits	e.g. visits to specialized PTSD clinics or to primary care clinics
Acute psychiatric care use	e.g. emergency department visits for psychiatric indications or psychiatric hospitalizations

Residential treatment	e.g. stays in residential PTSD or substance abuse programs
Psychiatric Comorbidities	Psychiatric diagnoses in the two years preceding the baseline PCL measurement

[a]EBP use was measured with a natural language processing algorithm that classifies psychotherapy notes in individual and group delivery formats.[14]

Table 2: Characteristics of New Trials of Adequate Dose and Duration Evidence-Based Medications for PTSD, with aligned PCL Measurement, including start dates from October 1, 2016 through March 7, 2018

Number of AMTs Aligned with PCL Measurement Patients Contribute	
1, %(n)	94.2 (786)
2, %(n)	5.8 (48)
Number of Prior AMTs since October 1, 1999 (with or without PCL)	
0, %(n)	81.1 (676)
1, %(n)	15.0 (125)
2+, %(n)	4.0 (33)
Number of Prior Adequate PE or CPT Trials since October 1, 1999 (with or without PCL)	
0, %(n)	93.2 (777)
1, %(n)	6.2 (52)
2+, %(n)	0.6 (5)
Timing of PCL Measurement Relative to AMT	
Days from First Available PTSD Diagnosis to Baseline PCL, M (SD)	1,074.6 (1,378.7)
Days from Baseline PCL to Follow-Up PCL, M (SD)	80.8 (10.3)
Baseline PCL Score, M (SD)	57.8 (11.1)

Abbreviations. PTSD=posttraumatic stress disorder, PCL=PTSD Checklist, FY=Fiscal Year, AMT=Adequate Medication Trial (12 or more weeks of fluoxetine, sertraline, topiramate, paroxetine, or venlafaxine at required dose at a minimally adequate dose), PE=Prolonged Exposure, CPT=Cognitive Processing Therapy

Table 3: Comparison of New Trials of Adequate Dose and Duration Evidence-Based Medications for PTSD, with and without aligned PCL Measurement, including start dates from October 1, 2016 through March 7, 2018

	Trials without PCL Measurement (n=38,089)	Trials with PCL Measurement (n=834)
Concurrent Treatment		
Any PE, % (n)***	0.8 (319)	8.2 (68)
Sessions of PE, M (SD)*	3.6 (2.8)	4.5 (3.1)
Any Individual CPT, % (n)***	2.7 (1,018)	29.6 (247)
Sessions of Individual CPT, M (SD)***	3.6 (2.9)	5.2 (3.3)
Any Group CPT, % (n)***	1.1 (421)	8.4 (70)
Sessions of Group CPT, M (SD)*	4.6 (4.3)	5.8 (4.2)
Any Non-PE/CPT Individual Therapy, % (n)***	32.2 (12,264)	62.2 (519)
Any Non-CPT Group Therapy, % (n)***	15.2 (5,792)	30.9 (258)
Any Non-F/S/P/V Antidepressant, % (n)*	51.9 (19,749)	56.0 (467)
Any Non-Topiramate Anticonvulsant, % (n)	28.7 (10,924)	27.2 (227)
Any Sedative/Hypnotics, % (n)***	21.9 (8,334)	16.1 (134)
Any Opioid, % (n)***	13.5 (5,149)	9.0 (75)
Any Atypical Antipsychotic, % (n)	16.8 (6,380)	15.2 (127)
Any Prazosin, % (n)***	29.3 (11,143)	40.5 (338)
Any Naltrexone or Acamprosate, % (n)**	2.9 (1,097)	4.8 (40)
Any Opioid Replacement Therapy, % (n)	1.3 (483)	1.3 (11)
Primary Prescribing Clinician Characteristics		
Age, M (SD)**	51.0 (12.1)	49.6 (12.3)
Women, % (n)	37.9 (14,449)	37.1 (309)
Psychiatrist, % (n)*	40.9 (15,588)	45.2 (377)
Other Physician, % (n)***	31.8 (12,103)	22.2 (185)
Physician Assistant, % (n)	4.3 (1,651)	4.9 (41)
Nurse Practitioner, % (n)	18.0 (6,858)	18.6 (155)
Pharmacist, % (n)***	2.9 (1,120)	8.6 (72)
Percentage of Time Seeing PTSD Patients in Various Settings		
PTSD Service Section (PCT or residential), M (SD)***	5.7 (19.7)	9.4 (24.1)
Substance Abuse Service Section, M (SD)	2.5 (11.4)	2.1 (9.0)
General Mental Health Service Section, M (SD)***	76.7 (39.7)	82.7 (34.3)
Integrated Care Service Section, M (SD)***	5.6 (17.3)	8.1 (21.1)
Primary Care Service Section, M (SD)***	18.3 (37.3)	12.0 (31.1)
Patient Characteristics at Baseline		
Age, M (SD)***	46.5 (14.6)	40.9 (11.1)
Women, % (n)	16.9 (6,434)	16.1 (134)
Married, % (n)	54.9 (20,925)	55.8 (465)
Rural, % (n)	33.6 (12,789)	33.0 (275)
White Non-Hispanic, % (n)	63.2 (24,079)	60.8 (507)
Black Non-Hispanic, % (n)	20.6 (7,835)	18.1 (151)
Hispanic, % (n)***	9.2 (3,491)	13.3 (111)
OEF/OIF/OND Veteran, % (n)***	48.7 (18,533)	68.9 (575)
Vietnam Veteran, % (n)***	11.9 (4,535)	4.0 (33)
Combat Exposure, % (n)***	42.2 (16,069)	49.9 (416)
Sexual Trauma while in Military, % (n)	14.9 (5,688)	15.1 (126)
VA Disability Level 70% or Greater, % (n)	49.7 (18,933)	50.8 (424)
Service Use Characteristics in the 1 Year Preceding Baseline		

Any PTSD Outpatient Clinical Team Visits, % (n)***	19.1 (7,260)	33.7 (281)
Number of PTSD Outpatient Clinical Team Visits, M (SD)	9.6 (15.7)	9.6 (11.2)
Any Outpatient Mental Health Visits, % (n)	88.3 (33,612)	88.1 (735)
Number of Outpatient Mental Health Visits, M (SD)***	20.6 (42.1)	26.9 (45.5)
Any Outpatient Substance Abuse Visits, % (n)***	11.0 (4,205)	15.4 (128)
Number of Outpatient Substance Abuse Visits, M (SD)	22.9 (37.7)	21.9 (42.7)
Any Outpatient Primary Care Visits, % (n)***	87.9 (33,495)	82.1 (685)
Number of Outpatient Primary Care Visits, M (SD)***	7.1 (7.8)	6.0 (5.9)
Any ED Visits for Psychiatric Indication, % (n)	13.1 (4,979)	13.2 (110)
Number of ED Visit for Psychiatric Indication, M (SD)	2.1 (2.2)	1.8 (1.6)
Any Acute Inpatient Mental Health Treatment, % (n)**	8.6 (3,257)	11.3 (94)
Days of Acute Inpatient Mental Health, M (SD)	16.1 (24.8)	17.8 (23.3)
Any Residential PTSD Treatment, % (n)***	1.0 (364)	2.9 (24)
Days Residential PTSD Treatment, M (SD)	44.8 (40.7)	28.8 (21.0)
Any Residential Substance Abuse Treatment, % (n)	1.9 (728)	2.5 (21)
Days Residential Substance Abuse Treatment, M (SD)	43.2 (43.3)	39.3 (33.6)
Any Integrated Care Visits, % (n)***	26.5 (10,110)	35.3 (294)
Days Integrated Care Visits, M (SD)	3.9 (7.9)	3.1 (4.3)
Any Neurology Visits, % (n)	12.1 (4,596)	10.1 (84)
Days Neurology Visits, M (SD)	2.4 (2.3)	2.3 (1.8)
Any Sleep Clinic Visits, % (n)	14.7 (5,597)	14.6 (122)
Days Sleep Clinic Visits, M (SD)	2.2 (1.6)	2.3 (1.8)
Any Polytrauma TBI Specialty Clinic Visits, % (n)***	6.3 (2,379)	11.5 (96)
Days Polytrauma TBI Specialty Clinic Visits, M (SD)	4.7 (13.7)	3.3 (4.7)
Comorbidities in the 2 Years Preceding Baseline		
Pain Disorder, % (n)	80.7 (30,749)	80.9 (675)
Headache Disorder, % (n)***	31.4 (11,974)	36.9 (308)
Psychotic Disorders, % (n)***	3.8 (1,449)	1.6 (13)
Bipolar Mood Disorders, % (n)*	8.2 (3,103)	6.0 (50)
Depressive Mood Disorders, % (n)***	73.0 (27,802)	80.8 (674)
Anxiety Disorders, %(n)	46.8 (17,840)	50.0 (417)
Traumatic Brain Injury, % (n)***	8.6 (3,267)	14.8 (123)
Alcohol Use Disorders, % (n)***	27.6 (10,522)	33.3 (278)
Opioid Use Disorders, % (n)*	5.7 (2,176)	7.3 (61)
Other Substance Use Disorders, % (n)***	16.6 (6,337)	21.0 (175)

*p<0.05, **p<0.01, ***p<0.001

Abbreivations. PTSD=posttraumatic stress disorder, PCL=PTSD Checklist, FY=Fiscal Year, PE=Prolonged Exposure, CPT=Cognitive Processing Therapy, F/S/P/V=Fluoxetine/Sertraline/Paroxetine/Venlafaxine, PCT=PTSD Care Team, OEF/OIF/OND=Operations Enduring Freedom/Iraqi Freedom/New Dawn, VA=Department of Veterans Affairs.

Table 4: Weighted Outcomes for Patients with an Adequate Trial of an Effective Medication for PTSD plus PCL Measurement

Agent	Fluoxetine (n=228)	Paroxetine (n=87)	Sertraline (n=307)	Topiramate (n=96)	Venlafaxine (n=116)	Pairwise Differences*
Raw Outcomes						
Baseline PCL Score, M (SD)	58.5 (11.7)	58.4 (11.3)	57.5 (10.9)	58.3 (15.0)	58.6 (11.8)	No differences
Change in PCL, M (SD)	-8.1 (15.0)	-6.8 (16.0)	-7.5 (12.2)	-6.8 (14.0)	-10.1 (19.5)	No differences
Remission of PTSD, % (n)	2.9 (8)	0.0 (0)	4.7 (14)	1.3 (2)	10.9 (9)	FSTV≠P; FPST≠V; S≠T
Symptom Clusters						
Baseline Reexperiencing, M (SD)	14.4 (3.6)	14.4 (3.6)	14.3 (3.8)	15.1 (3.5)	14.3 (3.9)	No differences
Change in Reexperiencing, M (SD)	-1.8 (4.2)	-1.6 (4.9)	-1.8 (3.6)	-1.8 (4.5)	-2.1 (5.2)	No differences
Baseline Avoidance, M (SD)	6.5 (1.5)	6.3 (1.8)	6.3 (1.6)	6.4 (1.8)	6.2 (1.9)	No differences
Change in Avoidance, M (SD)	-1.1 (2.4)	-0.8 (2.2)	-0.7 (1.8)	-0.7 (2.9)	-1.0 (2.6)	No differences
Baseline NACM, M (SD)	19.9 (4.6)	19.5 (5.6)	19.4 (5.2)	19.5 (6.0)	20.6 (5.3)	No differences
Change in NACM, M (SD)	-2.8 (6.2)	-2.4 (6.2)	-2.5 (5.1)	-2.2 (5.5)	-4.2 (7.6)	No differences
Baseline Hyperarousal, M (SD)	17.4 (3.9)	17.9 (3.8)	17.3 (3.9)	17.2 (7.1)	17.2 (4.7)	No differences
Change in Hyperarousal, M (SD)	-2.5 (5.2)	-2.1 (5.6)	-2.5 (4.0)	-2.1 (5.1)	-2.8 (6.2)	No differences
Baseline Sleep, M (SD)	6.0 (1.8)	6.1 (1.6)	6.2 (1.7)	6.3 (1.9)	6.1 (1.8)	No differences
Change in Sleep, M (SD)	-0.7 (2.1)	-0.8 (2.3)	-1.1 (1.8)	-0.9 (2.3)	-0.9 (2.7)	No differences

*Significant Differences are assessed at $p<0.05$ for the Omnibus comparison, with pair-wise testing where indicated.

Abbreviations. PTSD=Posttraumatic Stress Disorder, PCL=PTSD Checklist, NACM=Negative Alterations in Cognitions and Mood

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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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
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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

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

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Measurement Strategies for Evidence-Based Psychotherapy 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 delivery of psychotherapy for posttraumatic stress disorder (PTSD) that is both consistent with the underlying evidence supporting psychotherapy as a treatment for PTSD and associated with the best levels of symptom improvement. We quantified psychotherapy 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. Quality of psychotherapy for PTSD in the VA improved over time.

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

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

Posttraumatic stress disorder (PTSD) is a mental health condition that may follow exposure to a traumatic event (American Psychiatric Association, 2013). Symptoms include reexperiencing the trauma, avoidance of reminders of the trauma, arousal, 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). The VA has implemented multiple effective treatments for PTSD, including two specific evidence-based psychotherapy (EBP) protocols (Karlin & Cross, 2014): Cognitive Processing Therapy (CPT) and Prolonged Exposure (PE). CPT is comprised of twelve weekly 60-minute sessions of cognitive therapy, during which veterans address maladaptive thoughts associated with their worst traumatic event (Patricia A. Resick, Monson, & Chard, 2017). CPT can be administered either in an individual therapy format or a group format (P. A. Resick et al., 2015). PE consists of nine to twelve weekly 90-minute sessions of trauma-associated imaginal and in-vivo exposures administered in an individual therapy format (Foa, Hembree, & Rothbaum, 2007). Research trials of CPT and PE have resulted in statistically significant and clinically meaningful improvement in veterans' PTSD symptoms (Haagen, Smid, Knipscheer, & Kleber, 2015). The VHA Uniform Mental Health Services Package mandated the availability of these treatments in VHA clinics beginning in 2008 (Kussman, 2008).

Measuring the implementation of EBPs for PTSD has been a challenge. Single-site studies have used labor-intensive chart review to identify psychotherapy notes indicating the

provision of EBPs (Hundt et al., 2015; Kehle-Forbes, Meis, Spoont, & Polusny, 2016; Lamp, Maieritch, Winer, Hessinger, & Klenk, 2014; Lu, Plagge, Marsiglio, & Dobscha, 2016; Mott, Mondragon, et al., 2014; Mott, Stanley, Street, Grady, & Teng, 2014; Shiner, Bateman, et al., 2012). Studies attempting to measure implementation of EBPs for PTSD nationally have relied on use of psychotherapy procedural codes (Cully et al., 2008; Mott, Hundt, Sansgiry, Mignogna, & Cully, 2014), with some assumptions about how the number and timing of encounters indicate that an EBP could have been delivered (Seal et al., 2010; Spoont, Murdoch, Hodges, & Nugent, 2010). For example, Spoont et al. (2010) measured whether patients had at least eight encounters associated with a psychotherapy procedural code over the course of 6 months (Spoont et al., 2010), while Seal et al. (2010) determined whether those encounters occurred over the course of 15 weeks (Seal et al., 2010). However, assumptions about the use of psychotherapy procedural codes may be incorrect, as these codes are not protocol-specific.

We have performed three studies using automated natural language processing (NLP) of psychotherapy notes to bridge the gap between laborious chart review and efficient but potentially inaccurate use of psychotherapy procedural codes. NLP is a method to abstract information from large unstructured bodies of note text (Meystre, Savova, Kipper-Schuler, & Hurdle, 2008). Our general approach has been to use machine learning to train a computer to mimic the judgments of expert clinicians in classifying clinical notes (Hripcsak & Wilcox, 2002); in our case, practicing therapists classify whether a psychotherapy note describes the provision of an EBP for PTSD. In our initial (single-site) study, we found that in 43% of encounters with psychotherapy procedural codes, the associated notes described services other than psychotherapy, such as intakes, psychological testing, and case management services (Shiner, D'Avolio, et al., 2012). This raised concerns about the accuracy of psychotherapy

procedural codes. In our second (regional) study of 1,924 patients enrolling in six specialized outpatient PTSD clinics, patients had a mean of 9.1 encounters with psychotherapy procedural codes over their initial six months of treatment, but only 0.4 of these were EBP sessions (Shiner et al., 2013). Importantly, 6.1% (n=121) patients received at least one EBP session. This showed both that having a given number of encounters was not a proxy for receiving EBP and that it is possible to measure EBP delivery with an automated NLP-based classifier. In our third (national) study of 255,933 Iraq and Afghanistan Veterans, we found that 20.2% (n=51,852) received at least one EBP session over a median of 4.1 years of observation (Maguen et al., 2018). This showed we could efficiently apply an automated NLP-based classifier to a large national population. However, in focusing on Iraq and Afghanistan Veterans, this study examined only a subset of VA patients with PTSD. Additionally, this work did not examine the adequacy of treatment for patients who received EBP.

Donabedian (1997) proposed a framework for measuring healthcare quality that divides measures into domains of structure, process, and outcome (Donabedian, 1997). In Donabedian's model, a quality measure assessing whether patients with PTSD received an EBP would fall under the process domain. Such process measures would allow healthcare teams to assess the effectiveness of their efforts to improve the quality of care that they deliver. For example, staff members at a VA mental health clinic trying to increase the number of patients who receive EBP for PTSD might use such a process measure to understand whether their improvement intervention has worked. However, this model is predicated upon the validity of the quality measure. 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. In the case of EBP for PTSD, the receipt of at least one session is an insufficient measure of quality

because the studies establishing the efficacy of EBP for PTSD typically require multiple weekly sessions delivered by the same therapist over several months. Therefore, now that we can classify whether encounters associated with psychotherapy procedural codes include the provision of EBP, the next step is to examine the effect of increased measurement requirements designed to better approximate the evidence-based care process.

This study expands our work to all veterans who initiated PTSD care in VA from 2004 through 2013. This was a time of intense demographic change (Hermes, Rosenheck, Desai, & Fontana, 2012; Rosenheck & Fontana, 2007) and resource reallocation (Wagner, Sinnott, & Siroka, 2011) in VA, with a national focus on improving the capacity of the VA mental health treatment system to deliver evidence-based treatments (Karlin & Cross, 2014; Rosen et al., 2016). Our objectives were to: (1) measure the delivery of EBPs for PTSD to a national cohort of Veterans from diverse service eras; (2) determine longitudinal trends in EBP for PTSD delivery according to potential quality measures; and (3) determine whether quality measures that more stringently reflect the evidence supporting EBPs are associated with superior outcomes. While the VA has operationalized an EBP reporting strategy that leverages therapist-completed medical record templates (Sripada, Bohnert, Ganoczy, & Pfeiffer, 2018), our prior work has shown that uptake of the templates has lagged therapist-reported use of EBPs (Shiner, Leonard Westgate, et al., 2018). As efforts to incentivize the use standardized reporting tools such as templates are implemented (Sripada, Pfeiffer, Rauch, Ganoczy, & Bohnert, 2018), we feel that our work leveraging historical data will be informative to the VA and other large healthcare systems as they look to leverage these diverse data sources to develop valid quality measures to help drive improvement (Brown, Scholle, & Azur, 2014; Hepner et al., 2016).

Method

Data Source

We used the VA corporate data warehouse (CDW) to identify patients with new PTSD treatment episodes from fiscal year 2004 (FY04) through FY13. We obtained patient demographic information as well as encounter, diagnostic, patient-reported outcome, and pharmacy data from the CDW. The Veterans Institutional Review Board of Northern New England 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).

Evidence-Based Psychotherapy for PTSD Receipt

We identified all encounters associated with psychotherapy procedural codes for each patient during the one-year period of observation and linked these encounters to the related treatment notes. This resulted in a set of 18,185,216 documents. We used our previously-developed NLP-based classifier, which has an overall classification accuracy of 0.92 (Maguen et

al., 2018), to determine whether each document described the provision of psychotherapy at all, whether psychotherapy documents described the provision of PE or CPT, and whether CPT was delivered in a group or an individual format (CPT-G, CPT-I). We found that 0.5% (n=88,674) of documents described PE, 0.8% (n=143,147) of documents described CPT-G, 1.2% (n=217,250) of documents described CPT-I, 30.6% (n=5,558,844) of documents described other group or individual psychotherapy, and 67.0% (n=12,177,301) of documents did not describe psychotherapy at all.

Measures of Psychotherapy Quality

We followed a series of progressively restrictive steps in calculating our putative measures of psychotherapy quality. First, we used the NLP-based classifier results to determine whether each patient received any psychotherapy, any individual psychotherapy, any group psychotherapy, as well as each of the EBPs during their initial year of treatment based on their clinical notes. Second, we added a requirement that patients had an "adequate" number of psychotherapy sessions, defined here as eight or more sessions. Outcomes research in psychotherapy for anxiety and depressive disorders has indicated that half of patients achieve a clinically meaningful improvement after eight sessions (Howard, Kopta, Krause, & Orlinsky, 1986). Similarly, most patients who respond to evidence-based psychotherapies for PTSD have achieved the bulk of their gains by session eight (Galovski, Blain, Mott, Elwood, & Houle, 2012; Tuerk et al., 2011). Third, we added a requirement that the eight sessions be delivered by the same therapist. Continuity of care is associated with improved health outcomes across disorders (van Walraven, Oake, Jennings, & Forster, 2010), and in mental health treatment in particular (Adair et al., 2005). For group therapy led by two-therapist teams, each therapist was considered separately for meeting this requirement. Fourth, we added a requirement that eight sessions be

delivered during a 14-week period. Because both PE and CPT are designed for delivery in a weekly or twice-a-week format (Foa et al., 2005; P. A. Resick, Nishith, Weaver, Astin, & Feuer, 2002), this requirement ensures that the sessions are spaced in a similar manner to the efficacy trials supporting clinical practice, while allowing some flexibility for missed or rescheduled sessions. This treatment density standard has been used as part of VA psychotherapy performance measures (Trafton et al., 2013).

Concurrent Evidence-Based Medication for PTSD Receipt

We determined whether patients also received adequate trials of evidence-based medications for PTSD. To do this, 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 determined whether patients received one of the four effective antidepressants for PTSD specifically recommended in the VA/Department of Defense Clinical Practice Guideline (VA/DoD CPG) in place during the time our cohort received treatment (Friedman, Lowry, & Ruzek, 2010). These included fluoxetine, paroxetine, sertraline, and venlafaxine. For patients who received one of the four effective antidepressants for PTSD, we determined whether they received an adequate treatment, which we defined as eight weeks of a daily dose at least as high as the dose used in the efficacy trials supporting the treatment recommendation (Jonas et al., 2013; Watts et al., 2013). While the length of efficacy trials of psychotropic medications for PTSD varies, the VA/DoD CPG recommended medication trials of at least eight weeks (Friedman et al., 2010). Therefore, participants receiving continuous treatment of one of the following medications daily for eight weeks or more were considered to

have received an adequate medication trial (AMT): fluoxetine 20 mg or more daily, paroxetine 20 mg or more daily, sertraline 100 mg or more daily, and venlafaxine 150 mg or more daily.

Covariates

We developed three groups of covariates. First, we examined patient characteristics, such as age, gender, race, military service era, rurality, military-related exposures (including combat and sexual trauma), and medical and psychiatric comorbidities. Second, we examined health service use characteristics including prior receipt of psychotherapy, outpatient visits, emergency department visits, and admissions. For prior receipt of psychotherapy, we assessed whether patients had an outpatient encounter associated with psychotherapy procedural codes in the two years prior to their index PTSD diagnosis. Outpatient visits included visits to specialized PTSD clinics, general mental health clinics, substance abuse clinics, and integrated primary care-mental health clinics. Emergency department visits included those for a psychiatric indication. Admissions included stays on an acute inpatient psychiatric clinic, a residential PTSD treatment program, or a residential substance abuse program. Third, we examined therapist characteristics. Patients were assigned a primary therapist based on the clinician who completed the plurality of their psychotherapy encounters. Primary therapists were characterized by age, gender, service section, and professional background. Service section included specialized PTSD, general mental health, substance abuse, and primary care-mental health integration clinics. Because individual therapists 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 therapists 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. Professional background included psychologist, social worker, nurse, and

psychiatrist. To account for the possibility that some psychotherapy might be delivered briefly in the course of medication management, we assessed whether each provider had prescription privileges.

Patient-Reported Outcomes Assessment

Use of patient-reported outcome measurement using the PTSD Checklist (PCL; Weathers, Litz, Herman, Huska, & Keane, 1993) as part of routine practice became more common beginning in FY08 (Shiner, Westgate, 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, or DSM-IV (American Psychiatric Association, 2000; Wilkins, Lang, & Norman, 2011). 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 meet minimal symptomatic criteria for PTSD according to DSM-IV, defined as 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 on the PCL (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 had at least one encounter that was administratively coded as psychotherapy with those who did not using t-test or χ^2 analysis, as appropriate. We then described psychotherapy receipt as measured using both administrative coding and the NLP-based clinical note classification algorithm for the entire cohort during each fiscal year and for the overall 10-year period. We then focused on psychotherapy initiation by excluding patients who had encounters that were administratively coded as psychotherapy in the two years prior to their index PTSD diagnosis and recalculated initiation rates for each psychotherapy category for each individual fiscal year and for the overall 10-year period. We progressively added the measures of psychotherapy quality described above to this sub-cohort newly initiating psychotherapy, representing the cumulative number of patients who met each increasingly restrictive standard during their first year of PTSD treatment.

For causal analyses using patients from the FY08-13 portion of the cohort, we identified patients who initiated EBP at progressively higher levels of adherence to our "quality" measures (8 visits, 8 visits with the same therapist, 8 visits with the same therapist within 14 weeks) and had concurrent symptoms measurement using the PCL, as defined below. 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 at or before the second session (baseline) but no more than 14 days prior to the first session, and at or after the seventh session (follow-up) but no more than 14 days after the eighth session. 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 session 1. When there were multiple PCL scores meeting our follow-up criterion, we selected the measure closest to session 8. We calculated two change measures from baseline to follow-up: 1) mean PCL change, and 2) "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 (Shiner, Westgate, 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 reliable change and loss of diagnosis criteria. Given that we were comparing three conditions (8 visits, 8 visits with the same therapist, 8 visits with the same therapist within 14 weeks), we used a conservative Bonferroni-corrected alpha of $p<0.0167$ for pre/post comparisons to avoid type I error. We balanced patient characteristics that have a plausible association with the outcome using inverse propensity of treatment weighting (IPTW; Stuart, 2010). 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 variables that have a plausible correlation with the outcome. Using these propensity scores, we weighted participants in order to balance the pretreatment covariate distribution. Covariates in the IPTW model included baseline PCL score, number of days between the baseline PCL and session 1, number of days between follow-up PCL and session 8, and all covariates described in Table 1. In balancing almost 50 patient characteristics, 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 our results 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 to measure the change in slope over time among the tree treatment groups. The model is weighted by the inverse of the propensity scores and adjusted for any unbalanced covariates ($p<0.01$). 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, 88.6% (n=647,513) had at least one psychotherapy procedural code during their first year of PTSD treatment. Patients who did and did not receive a

psychotherapy procedural code differed on almost all variables (Table 1). Most prominently, those who received a psychotherapy procedural code were more likely to be women, to have experienced sexual trauma while in the military, and to have comorbid psychiatric and substance abuse diagnoses. At the same time, they were less likely to be rural or to have been exposed to combat. They also received other VA health services at higher levels, and importantly, 47.1% (n=305,132) also received a psychotherapy procedural code in the two years prior to their index PTSD diagnosis. Almost half of patients who received a psychotherapy procedural code saw a woman as their primary therapist, and patients most commonly saw a psychologist or social worker as their primary therapist. In over a third of cases, the primary therapist had prescription privileges, indicating that therapy could have been coded as part of medication management. Patients primary therapists generally spent most of their time in general mental health settings, followed by specialized PTSD settings.

In the overall cohort, use of any psychotherapy, whether classified using procedural codes or natural language processing, increased over the 10-year period of examination (Table 2). While the percentage of patients receiving at least one psychotherapy procedural code had little room for improvement, the difference between receipt of any psychotherapy as measured using procedural codes and as measured using NLP decreased from FY04-05 (86.0% versus 54.7%) to FY12-13 (90.2% versus 65.8%). At the same time, the mean number of psychotherapy encounters remained stable (9.3 versus 10.0). This indicates that despite persistence of procedural coding discrepancies, more patients with PTSD were actually receiving psychotherapy during administratively coded psychotherapy encounters by the end of the period of examination. Furthermore, there was a dramatic increase in the use of EBP for PTSD, from

0.7% in FY04-05 to 14.1% in FY12-13. The most common EBP modality was individual CPT-I, followed by CPT-G, and PE.

We then applied quality standards to psychotherapy receipt among the 54.1% (n=396,032) of patients initiating psychotherapy after their index PTSD diagnosis. This resulted in a decrease in the percentage of patients who met those standards as the standards became more stringent (Table 3). For example, while 86.5% received at least one procedural code for psychotherapy in their first year of treatment, only 13.8% received eight or more sessions (as measured using procedural codes) over the course of any 14-week period. Similarly, if we use NLP rather than procedural codes to classify psychotherapy receipt, the figure drops from 13.8% to 11.4%. If we then require that NLP indicates the sessions are EBP, the figure drops from 11.4% to 2.0%. Therefore, estimates of psychotherapy receipt appear to be highly dependent on both the restrictiveness of the quality standards and the content of the psychotherapy notes. Despite these caveats, quality as determined by all standards we applied improved over time during the period of examination (Appendix 1).

A substantial number of patients from the FY08-13 cohort who met our increasingly restrictive quality standards had PCL measurement aligned with sessions 1 and 8 and were included in analyses comparing outcomes among patients who met increasingly strict quality standards. Among the 10,765 patients who had 8 or more sessions of EBP as measured using NLP, 19.1% (n=2,052) met our PCL-based inclusion criteria. Table 4 shows that there were few significant differences among patients who had 8 or more sessions of EBP with and without aligned PCL measurement. Furthermore, where differences were significant, the magnitude was small. After applying the IPTW procedure to balance covariates across quality standard groups,

only one unbalanced variable remained (Appendix 2): days between baseline PCL and session 1. This unbalanced variable was used as a covariate in weighted analyses.

In pre/post causal analyses, the most stringent quality standard (8 EBP sessions with the same therapist within 14 weeks) was associated with significantly higher rates of loss of diagnosis (23.3% versus 13.8%; p=0.0004, e=2.78) and continuous improvement on the PCL (-9.3 versus -7.1; p=0.0101, e=1.60) than the least stringent standard (any 8 EBP sessions during the first year of treatment, but not the second most stringent quality standard (8 EBP sessions with the same therapist during the first year of treatment). However, the second most stringent quality standard was not significantly superior to the least stringent quality standard, indicating that across data sources, only the strictest definition of treatment adequacy was consistently associated with superior pre/post outcomes. The e-value findings indicate that it would take a very strong unmeasured confounder (relative risk of 2.78 or greater) to overturn the loss of diagnosis finding and a moderately strong unmeasured confounder (relative risk of 1.60 or greater) to overturn the continuous improvement on the PCL finding. Our GLMM approach supports this assessment (Figure 1). The rate of improvement in PCL score was best when using the most stringent treatment adequacy standard. Thus, requiring a quality standard of 8 or more sessions with the same therapist within 14 weeks was associated with both the greatest amount of pre/post change and the fastest rate of change.

Discussion

We found that psychotherapy for PTSD quality standards that more stringently reflect the underlying evidence were associated with superior outcomes in clinical practice. Thus, our work provides preliminary validity for an NLP-based quality measure comprising eight or more

sessions of EBP, delivered by the same therapist, over the course of 14 weeks. The percentage of VA patients with new PTSD treatment episodes meeting this standard improved from 0.1% to 3.7% over a 10-year period marked by investment in mental health services from 2004 through 2013. This improvement is likely a reflection of the resources invested in the national implementation of EBP for PTSD. However, these findings highlight that while most patients initiating PTSD care in the VA did receive some psychotherapy in the initial year, the vast majority did not meet this quality standard. Thus, it is possible that many patients initiating care during this period would have benefited from more intensive treatment. This work shows that by examining the content of psychotherapy sessions, it is possible to avoid overestimating treatment quality, providing a more accurate baseline against which to measure the effect of improvement efforts. Regardless of how session content is measured in the future (e.g., NLP of note text versus the use of EBP-specific note templates), our work provides a basic framework for using the related data to develop an EBP for PTSD quality measure.

Our study addresses several gaps in the available research regarding quality measurement for PTSD treatment. First, few studies include clinical detail from chart notes, such as whether an EBP was delivered (Hepner et al., 2016). By using NLP, we were able to identify when an EBP was delivered for each person in the cohort and incorporate this information into our quality measures. Similarly, most measures of psychotherapy focus on access to care or quantifying the number of visits, and often this is due to limited data on diagnosis, severity of illness, treatment history, and the content and number of visits (Brown, Scholle, & Azur, 2014). Availablity of these additional factors in our dataset allowed us to perfom causal analyses in order to determine whether various definitions of quality were associated with improved PTSD outcomes.

There are several limitations to our study. First, we did not examine a range of cutoffs for the required number of sessions and for number of weeks over which those sessions should be delivered. Examining multiple cutoffs would have created an unmanageable number of comparisons, across which we would have had to balance our covariates to avoid bias in causal analyses. Thus, we used a single standard for number of sessions supported by prior research and a single standard for treatment density that has been used operationally in the VA. Future research should address the question of the minimal number of sessions for an adequate treatment and the maximum amount of time over which those sessions should be delivered. Second, we did not compare EBP to non-EBP. Extensive available research already demonstrates that trauma-focused evidence-based psychotherapy for PTSD is associated with superior outcomes to non-specific psychotherapy in the treatment of PTSD (The Management of Posttraumatic Stress Disorder Work Group, 2017). While additional "real world" studies about the clinical effectiveness of EBPs for PTSD (compared to other treatments) may be warranted, our work is not designed to make those inferences. Fourth, there were several differences in potentially important patient and therapist characteristics among those meeting various quality standards. However, analyses controlled for key differences and our sensitivity analyses indicate that unmeasured confounding is unlikely to overturn our outcome. Finally, even NLP of psychotherapy notes to detect EBP use is a proxy measure of EBP delivery. Without video, we cannot be sure what happened during psychotherapy sessions. However, we believe that our NLP method is the closet possible approximation to study EBP implementation in the VA during the critical time period examined.

In summary, this research demonstrates that a theoretically-oriented approach to quality measurement can be used to create the basic structure of a psychotherapy for PTSD quality

measure. While our work captures the receipt of effective and timely treatment, our measure of quality is incomplete. Health systems should also seek to provide PTSD care that is safe, patient-centered, equitable, and efficient (Pincus et al., 2007).

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Table 1: VA Users with New Episodes of PTSD Care from 2004-2013, by Receipt of Psychotherapy Procedure Code

		Category	
	Overall	Received Psychotherapy	Did Not Receive Psychotherapy
Patient Characteristics, N	731,520	647,513	84,007
Age, M (SD)**	49.9 (15.4)	49.8 (15.2)	50.8 (16.5)
Women, % (n)**	8.5 (61,853)	8.9 (57,409)	5.3 (4,444)
Married, % (n)	53.2 (389,262)	53.0 (342,970)	55.1 (46,292)
White Non-Hispanic, % (n)*	62.6 (457,673)	62.5 (404,774)	63.0 (52,899)
OEF/OIF/OND Veteran, % (n)**	28.5 (208,769)	28.5 (184,246)	29.2 (24,523)
Rural, % (n)**	35.3 (258,177)	34.8 (225,529)	38.9 (32,648)
Combat Exposure, % (n)**	32.8 (239,686)	32.1 (208,007)	37.7 (31,679)
Sexual Trauma while in Military, % (n)**	9.2 (67,024)	9.6 (62,388)	5.5 (4,636)
VA Disability Level 70% or Greater, % (n)	59.0 (431,632)	58.9 (381,621)	59.5 (50,011)
Charleson Comorbidity Index 1 or greater, % (n)**	24.4 (178,575)	24.3 (157,342)	25.3 (21,233)
Psychotic Disorders, % (n)**	5.7 (41,789)	5.9 (38,243)	4.2 (3,546)
Bipolar Mood Disorders, % (n)**	7.2 (52,596)	7.6 (49,128)	4.1 (3,468)
Depressive Mood Disorders, % (n)**	65.5 (478,763)	67.2 (435,185)	51.9 (43,578)
Non-PTSD Anxiety Disorders, % (n)**	34.5 (252,107)	35.8 (231,968)	24.0 (20,139)
Traumatic Brain Injury, % (n)**	8.6 (62,936)	7.8 (56,844)	7.3 (6,092)
Alcohol Use Disorders, % (n)**	27.1 (198,166)	28.1 (182,205)	19.0 (15,961)
Opioid Use Disorders, % (n)**	3.7 (27,175)	4.0 (25,786)	1.7 (1,389)
Other Drug Use Disorders, % (n)**	19.7 (144,350)	20.7 (134,050)	12.3 (10,300)
Service Use Characteristics, N	731,520	647,513	84,007
Prior Psychotherapy Use (2 years), % (n)**	45.9 (335,488)	47.1 (305,132)	36.1 (30,356)
Adequate Trial of EBA for PTSD, % (n)**	31.4 (229,849)	28.4 (207,632)	26.5(22,217)
PTSD Outpatient Clinical Team Use (540 or 561), % (n)**	34.9 (255,151)	36.7 (237,541)	21.0 (17,610)
Outpatient Mental Health Visits, M (SD)**	12.6 (15.1)	13.6 (15.6)	4.3 (5.1)
Outpatient Substance Abuse Visits, M (SD)**	3.0 (13.1)	3.4 (13.8)	0.4 (4.1)
Outpatient Primary Care Visits, M (SD)**	3.5 (3.5)	3.5 (3.5)	2.9 (3.0)
Emergency Department Visit for Psychiatric Indication, % (n)**	6.4 (46,616)	6.8 (43,781)	3.4 (2,835)
Acute Mental Health Inpatient Admission, % (n)**	6.6 (48,531)	7.2 (46,429)	2.5 (2,102)
Residential PTSD Admission, % (n)**	2.4 (17,278)	2.6 (16,836)	0.5 (442)
Residential Substance Abuse Admission, % (n)**	2.7 (19,696)	3.0 (19,464)	0.3 (232)
Primary Therapist Characteristics, where known			
Age, M (SD)	-	50.8 (11.2)	-
Women, % (n)	-	47.0 (304,190)	-
Psychologist, % (n)	-	29.3 (189,719)	-
Social Worker, % (n)	-	29.2 (189,056)	-
Nurse, % (n)	-	9.0 (58,347)	-
Psychiatrist, % (n)	-	25.7 (166,326)	-
Other, % (n)	-	6.7 (43,374)	-
Prescribing Privileges, % (n)	-	36.0 (233,108)	-
Percentage of Time Seeing PTSD Patients in Various Settings	-	-	-
PTSD Service Section (PCT or residential), M (SD)	-	28.5 (37.5)	-
Substance Abuse Service Section, M (SD)	-	5.7 (19.5)	-
Comorbid PTSD Substance Abuse Service Section, M (SD)	-	0.2 (3.4)	-
General Mental Health Service Section, M (SD)	-	54.7 (39.9)	-
Integrated Care Service Section, M (SD)	-	6.5 (18.8)	-

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; *p<0.05, **p<0.001

Table 2: Psychotherapy Receipt in the in the Year Following Initial PTSD Diagnosis						
Fiscal Year	2004-2005	2006-2007	2008-2009	2010-2011	2012-2013	Overall
New PTSD Episodes	n=111,828	n=128,652	n=160,444	n=168,771	n=161,825	731,520
Total Psychotherapy Encounters, M (SD)	9.3 (14.1)	8.8 (13.3)	9.4 (13.7)	10.1 (14.0)	10.0 (13.7)	9.6 (13.8)
Any Receipt						
Any Psychotherapy: Procedure Codes	86.0% (96,138)	86.8% (111,703)	88.0% (141,227)	90.3% (152,407)	90.2% (146,038)	88.5% (647,513)
Individual	81.7% (91,337)	82.8% (106,554)	84.9% (136,279)	87.3% (147,301)	86.8% (140,415)	85.0% (621,886)
Group	32.0% (35,734)	30.3% (39,042)	29.3% (46,999)	31.7% (53,426)	33.5% (54,164)	31.4% (229,365)
Any Psychotherapy: NLP	54.7% (61,224)	57.0% (73,393)	60.7% (97,422)	64.2% (108,317)	65.8% (106,523)	61.1% (446,879)
Individual	43.6% (48,735)	46.9% (60,329)	52.0% (83,354)	54.9% (92,691)	56.5% (91,360)	51.5% (376,469)
Group	27.3% (30,478)	26.6% (34,275)	26.2% (42,047)	29.0% (48,913)	30.6% (49,559)	28.1% (205,272)
Any EBP: NLP	0.7% (773)	2.5% (3,210)	7.4% (11,940)	11.1% (18,754)	14.1% (22,756)	7.9% (57,433)
Group Cognitive Processing Therapy	0.2% (257)	0.7% (940)	2.2% (3,587)	3.9% (6,541)	4.5% (7,203)	2.5% (18,528)
Individual Prolonged Exposure	0.1% (162)	0.3% (350)	1.6% (2,608)	3.1% (5,192)	3.6% (5,874)	1.9% (14,186)
Individual Cognitive Processing Therapy	0.4% (453)	1.9% (2,431)	4.8% (7,726)	6.4% (10,726)	8.6% (13,860)	4.8% (35,196)

Note. PTSD=Posttraumatic Stress Disorder; EBP=Evidence-Based Psychotherapy for PTSD; NLP=Natural Language Processing

Table 3: Psychotherapy Initiation in the Year Following Initial PTSD Diagnosis among 396,032 Patients with No Psychotherapy Encounters in the 2 Years Prior to PTSD Diagnosis, Fiscal Years 2004-2013; Mean of 7.8 (SD=10.8) psychotherapy encounters.

Quality Standard	Any Receipt	8+ Sessions	8+ Sessions, Same Therapist	8+ Sessions in 14 weeks, Same Therapist
Any Psychotherapy: Procedure Codes	86.5% (342,381)	32.2% (127,381)	23.3% (92,374)	13.8% (54,608)
Individual	82.7% (327,358)	21.9% (86,704)	14.6% (57,954)	6.1% (24,050)
Group	28.3% (112,152)	12.6% (49,832)	10.2% (40,346)	7.9% (31,403)
Any Psychotherapy: NLP	59.5% (235,706)	21.8% (86,238)	18.1% (71,789)	11.4% (44,963)
Individual	50.4% (199,543)	11.4% (45,110)	9.9% (39,182)	4.6% (18,176)
Group	25.0% (99,185)	11.1% (44,024)	8.9% (35,124)	6.7% (26,468)
Any EBP: NLP	7.7% (30,593)	2.9% (11,353)	2.5% (9,980)	2.0% (8,058)
Group Cognitive Processing Therapy	2.2% (8.815)	0.8% (3,300)	0.6% (2,226)	0.5% (1,867)
Individual Prolonged Exposure	2.1% (8,227)	0.6% (2,440)	0.6% (2,316)	0.5% (1,913)
Individual Cognitive Processing Therapy	4.7% (18,584)	1.4% (5,375)	1.3% (5,112)	1.0% (4,005)

Note. PTSD=Posttraumatic Stress Disorder; EBP=Evidence-Based Psychotherapy for PTSD; NLP=Natural Language Processing. Yearly trends presented in Appendix 1.

Table 4: VA Users Initiating Evidence-Based Psychotherapy for PTSD and Completing 8 or More Sessions within a Year, FY 2008-2013, by Receipt of Aligned PTSD Checklist Measurement

		Category	
	Overall	With Aligned PCL Measurement	Without Aligned PCL Measurement
Patient Characteristics, N	10,765	2,052	8,713
Age, M (SD)**	47.3 (15.2)	45.2 (15.2)	47.8 (15.1)
Women, % (n)	12.9 (1,390)	13.8 (283)	12.7 (1,107)
Married, % (n)*	60.8 (6,547)	62.8 (1,288)	60.4 (5,259)
White Non-Hispanic, % (n)	63.8 (6,871)	62.3 (1,279)	64.2 (5,592)
OEF/OIF/OND Veteran, % (n)**	41.7 (4,490)	50.3 (1,033)	39.7 (3,457)
Rural, % (n)	32.8 (3,529)	31.6 (649)	33.1 (2,880)
Combat Exposure, % (n)	27.7 (2,983)	27.0 (554)	27.9 (2,429)
Sexual Trauma while in Military, % (n)	13.2 (1,417)	13.5 (277)	13.1 (1,140)
VA Disability Level 70% or Greater, % (n)	58.8 (6,334)	60.2 (1,236)	58.5 (5,098)
Charleson Comorbidity Index 1 or greater, % (n)	12.6 (1,353)	12.3 (253)	12.6 (1,100)
Psychotic Disorders, % (n)	1.9 (209)	1.5 (31)	2.0 (178)
Bipolar Mood Disorders, % (n)	3.4 (363)	3.4 (70)	3.4 (293)
Depressive Mood Disorders, % (n)**	66.3 (7,141)	70.9 (1,455)	65.3 (5,686)
Non-PTSD Anxiety Disorders, % (n)*	37.9 (4,080)	41.0 (841)	37.2 (3,239)
Traumatic Brain Injury, % (n)**	15.6 (1,681)	18.6 (381)	14.9 (1,300)
Alcohol Use Disorders, % (n)*	24.6 (2,648)	26.5 (544)	24.2 (2,104)
Opioid Use Disorders, % (n)	1.9 (207)	2.1 (42)	1.9 (165)
Other Drug Use Disorders, % (n)	14.9 (1,607)	13.8 (283)	15.2 (1,324)
Service Use Characteristics, N			
Adequate Trial of EBA for PTSD, % (n)**	30.0 (3,227)	33.7 (691)	29.1 (2,536)
PTSD Outpatient Clinical Team Use (540 or 561), % (n)**	67.5 (7,270)	71.5 (1,467)	66.6 (5,803)
Outpatient Mental Health Visits, M (SD)*	28.6 (16.3)	27.8 (14.7)	28.8 (16.7)
Outpatient Substance Abuse Visits, M (SD)	3.8 (12.3)	4.2 (13.2)	3.8 (12.0)
Outpatient Primary Care Visits, M (SD)	3.3 (3.3)	3.3 (3.1)	3.3 (3.3)
Emergency Department Visit for Psychiatric Indication, % (n)	7.7 (829)	8.1 (166)	7.6 (663)
Acute Mental Health Inpatient Admission, % (n)	6.7 (722)	6.9 (141)	6.7 (581)
Residential PTSD Admission, % (n)	8.4 (904)	8.4 (173)	8.4 (731)
Residential Substance Abuse Admission, % (n)	2.4 (258)	2.2 (46)	2.4 (212)
Primary Therapist Characteristics, where known			
Age, M (SD)**	44.8 (10.9)	43.6 (11.1)	45.1 (10.8)
Women, % (n)	66.4 (5,825)	67.4 (1,126)	66.2 (4,699)
Psychologist, % (n)**	60.0 (6,450)	65.3 (1,339)	58.7 (5,111)
Social Worker, % (n)**	32.8 (3,529)	28.7 (588)	33.8 (2,941)
Nurse, % (n)*	2.2 (236)	1.3 (26)	2.4 (210)
Psychiatrist, % (n)*	1.6 (175)	0.8 (17)	1.8 (158)
Other, % (n)	3.4 (369)	3.9 (80)	3.3 (289)
Prescribing Privileges, % (n)*	8.9 (961)	7.6 (155)	9.3 (806)
Percentage of Time Seeing PTSD Patients in Various Settings	-	-	-
PTSD Service Section (PCT or residential), M (SD)*	56.2 (38.7)	58.3 (38.6)	55.6 (38.7)
Substance Abuse Service Section, M (SD)	3.7 (13.5)	3.5 (12.8)	3.7 (13.6)
Comorbid PTSD Substance Abuse Service Section, M (SD)**	0.4 (3.9)	0.9 (5.9)	0.3 (3.3)
General Mental Health Service Section, M (SD)*	30.7 (34.7)	28.6 (34.2)	31.2 (34.8)
Integrated Care Service Section, M (SD)	5.3 (16.1)	5.1 (16.1)	5.4 (16.1)

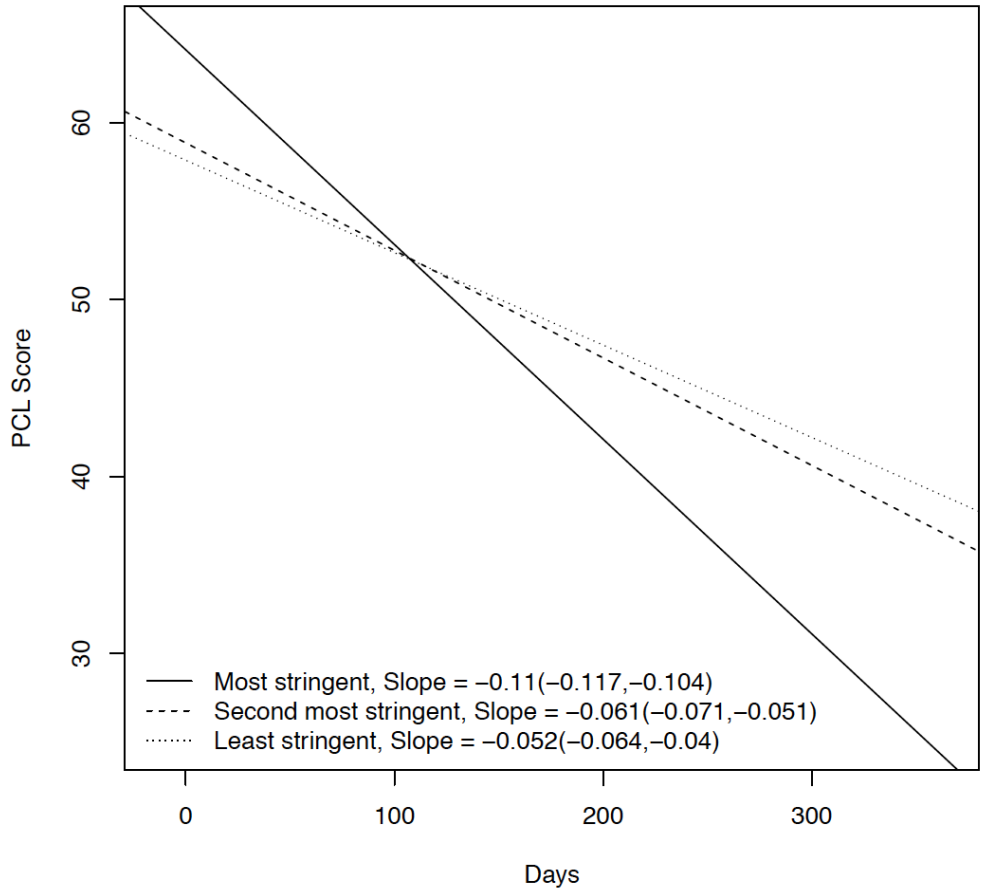
Note. VA=United States Department of Veterans Affairs; PTSD=Posttraumatic Stress Disorder; M=mean, SD=standard deviation; OEF/OIF/OND=Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn; *p<0.05, **p<0.001

Table 5: Inverse Propensity of Treatment Weighted Comparison of PTSD Symptomatic Outcomes for Patients Completing 8 or More Sessions of Evidence-Based Psychotherapy for PTSD with Aligned PTSD Checklist Measurement, FY 2008-2013, by Quality Standard

Quality Standard	(A) 8 n=303	(B) 8 ST n=549	(C) 8 ST 14W n=1,200	A versus B		A versus C		B versus C	
				P	E	P	E	P	E
Baseline PCL, mean (SD)	64.2 (11.0)	63.6 (10.1)	63.6 (10.0)	0.5383		0.4417		0.9994	
Change in PCL, mean (SD)	-7.1 (13.2)	-8.6 (14.2)	-9.3 (13.0)	0.1627	1.45	**0.0101**	1.60	0.3757	1.26
10-Poing Drop on PCL plus LOD, % (n)	13.8 (43)	21.4 (115)	23.3 (285)	0.0274	2.47	**0.0004**	2.77	0.4346	1.40

Note. E-value indicates the he 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; LOD=loss of diagnosis; **BOLD**=p<0.0167.

Figure 1: Repeated Measures Model of Change in Total PCL Score



Note. NLP=Natural Language Processing; EBP=Evidence-Based Psychotherapy for Posttraumatic Stress Disorder

APPENDIX 1: Psychotherapy Initiation in the Year Following Initial PTSD Diagnosis among Patients with No Psychotherapy Encounters in the 2 Years Prior to PTSD Diagnosis, by Punitive Quality Standards

Fiscal Years	2004-2005	2006-2007	2008-2009	2010-2011	2012-2013	Overall
New PTSD Episodes	n=58,061	n=69,640	n=90,269	n=92,515	n=85,547	396,032
Total Psychotherapy Encounters, M (SD)	8.0 (11.6)	7.5 (10.8)	7.7 (10.8)	8.0 (10.7)	7.9 (10.5)	7.8 (10.8)
Any Receipt						
Any Psychotherapy: Procedural Codes	84.4% (49,022)	85.2% (59,368)	85.9% (77,548)	88.1% (81,487)	87.6% (74,956)	86.5% (342,381)
Individual	79.6% (46,199)	81.0% (56,410)	82.6% (74,606)	84.8% (78,430)	83.8% (71,713)	82.7% (327,358)
Group	30.2% (17,540)	28.3% (19,714)	26.1% (23,591)	28.0% (25,933)	29.7 (25,374)	28.3% (112,152)
Any Psychotherapy: NLP	54.2% (31,496)	56.8% (39,537)	59.4% (53,589)	61.8% (57,182)	63.0% (53,902)	59.5% (235,706)
Individual	43.6% (25,307)	47.4% (32,978)	51.2% (46,204)	52.9% (48,939)	53.9% (46,115)	50.4% (199,543)
Group	25.6% (14,835)	24.6% (17,103)	23.1% (20,885)	25.4% (23,540)	26.7% (22,822)	25.0% (99,185)
Any EBP: NLP	0.6% (373)	2.7% (1,884)	7.7% (6,939)	10.7% (9,855)	13.5% (11,542)	7.7% (30,593)
Group Cognitive Processing Therapy	0.2% (104)	0.6% (436)	2.0% (1,801)	3.4% (3,160)	3.9% (3,314)	2.2% (8.815)
Individual Prolonged Exposure	0.1% (82)	0.3% (224)	1.9% (1,687)	3.2% (2,946)	3.8% (3,288)	2.1% (8,227)
Individual Cognitive Processing Therapy	0.4% (236)	2.1% (1,449)	4.9% (4,454)	6.0% (5,545)	8.1% (6,900)	4.7% (18,584)
Eight or More Sessions						
Any Psychotherapy: Procedural Codes	30.9% (17,926)	29.8% (20,757)	32.0% (28,864)	33.6% (31,079)	33.6% (28,755)	32.2% (127,381)
Individual	18.1% (10,506)	19.0% (13,214)	22.9% (20,635)	23.5% (21,741)	24.1% (20,608)	21.9% (86,704)
Group	15.4% (8,931)	13.1% (9,121)	11.5% (10,371)	12.4% (11,479)	11.6% (9,930)	12.6% (49,832)
Any Psychotherapy: NLP	19.3% (11,179)	19.6% (13,656)	21.3% (19,237)	23.4% (21,603)	24.0% (20,563)	21.8% (86,238)
Individual	7.0% (4,048)	8.8% (6,150)	11.9% (10,745)	12.8% (11,864)	14.4% (12,303)	11.4% (45,110
Group	12.6% (7,331)	11.4% (7,927)	10.3% (9,284)	11.4% (10,519)	10.5% (8,963)	11.1% (44,024)
Any EBP: NLP	0.2% (94)	0.7% (494)	2.6% (2,326)	4.4% (4,060)	5.1% (4,379)	2.9% (11,353)
Group Cognitive Processing Therapy	0.0% (23)	0.2% (109)	0.6% (579)	1.4% (1,337)	1.5% (1,252)	0.8% (3,300)
Individual Prolonged Exposure	0.0% (11)	0.0% (31)	0.5% (493)	1.1% (991)	1.1% (914)	0.6% (2,440)
Individual Cognitive Processing Therapy	0.1% (63)	0.5% (372)	1.4% (1,226)	1.8% (1,622)	2.4% (2,092)	1.4% (5,375)
Eight or More Sessions with the Same Therapist						
Any Psychotherapy: Procedural Codes	23.1% (13,389)	22.0% (15,288)	22.9% (20,635)	24.0% (22,204)	24.4% (20,858	23.3% (92,374)
Individual	11.8% (6,841)	12.5% (8,697)	15.2% (13,717)	15.6% (14,397)	16.7% (14,302)	14.6% (57,954)
Group	12.7% (7,367)	10.9% (7,595)	9.2% (8,317)	10.0% (9,237)	9.2% (7,830)	10.2% (40,346)
Any Psychotherapy: NLP	15.8% (9,167)	16.4% (11,389)	17.8% (16,028)	19.7% (18,189)	19.9% (17,016)	18.1% (71,789)
Individual	6.0% (3,456)	7.5% (5,216)	10.3% (9,302)	11.3% (10,464)	12.6% (10,744)	9.9% (39,182)
Group	10.2% (5,941)	9.4% (6,528)	8.2% (7,377)	9.1% (8,379)	8.1% (6,899)	8.9% (35,124)
Any EBP: NLP	0.1% (78)	0.7% (458)	2.3% (2,042)	3.9% (3,562)	4.5% (3,840)	2.5% (9,980)
Group Cognitive Processing Therapy	0.0% (11)	0.1% (74)	0.4% (369)	1.0% (924)	1.0% (848)	0.6% (2,226)
Individual Prolonged Exposure	0.0% (11)	0.0% (31)	0.5% (460)	1.0% (952)	1.0% (862)	0.6% (2,316)
Individual Cognitive Processing Therapy	0.1% (55)	0.5% (361)	1.3% (1,149)	1.7% (1,549)	2.3% (1,998)	1.3% (5,112)
Eight or More Sessions in 14 Weeks with the Same Therapist						
Any Psychotherapy: Procedural Codes	13.2% (7,678)	12.6% (8,747)	12.7% (11,437)	14.5% (13,390)	15.6% (13,356)	13.8% (54,608)
Individual	3.6% (2,074)	4.3% (2,971)	5.9% (5,345)	6.8% (6,300)	8.6% (6,300)	6.1% (24,050)
Group	9.6% (5,584)	8.4% (5,853	7.0% (6,304)	7.9% (7,297)	7.4% (6,365)	7.9% (31,403)
Any Psychotherapy: NLP	9.5% (5,497)	10.0% (6,962)	10.6% (9,540)	12.7% (11,763)	13.1% (11,201)	11.4% (44,963)
Individual	2.0% (1,154)	2.8% (1,983)	4.5% (4,068)	5.6% (5,176)	6.8% (5,795)	4.6% (18,176)
Group	7.2% (4,209)	7.0% (4,863)	6.0% (5,440)	7.1% (6,534)	6.3% (5,422)	6.7% (26,468)
Any EBP: NLP	0.1% (62)	0.5% (359)	1.7% (1,557)	3.2% (2,924)	3.7% (3,156)	2.0% (8,058)
Group Cognitive Processing Therapy	0.0% (8)	0.1% (61)	0.3% (302)	0.8% (777)	0.8% (719)	0.5% (1,867)
Individual Prolonged Exposure	0.0% (9)	0.0% (22)	0.4% (366)	0.9% (801)	0.8% (715)	0.5% (1,913)
Individual Cognitive Processing Therapy	0.1% (44)	0.4% (279)	0.9% (833)	1.3% (1,245)	1.9% (1,604)	1.0% (4,005)

Note. PTSD=Posttraumatic Stress Disorder; EBP=Evidence-Based Psychotherapy for PTSD; NLP=Natural Language Processing

Appendix 2: Raw and Weighted Covariates for Comparisons of Quality Standards for Patients Receiving 8 or More Sessions of Evidence-Based Psychotherapy for PTSD and Aligned PCL Measurement, FY 2008-2013

Patient Characteristics, N	Raw Data (A) 8 n=303	Raw Data (B) 8 ST n=549	Raw Data (C) 8 14W ST n=1,200	Raw Data p value	Weighted Data (A) 8 n=303	Weighted Data (B) 8 ST n=549	Weighted Data (C) 8 14W ST n=1,200	Weighted Data p value
Baseline PCL, M (SD)	64.9 (9.9)	63.2 (9.6)	63.5 (9.8)	0.041	64.2 (11.0)	63.6 (10.1)	63.6 (10.0)	0.735
Days Between Baseline PCL and Session 1, M (SD)	2.4 (15.5)	6.9 (23.0)	0.8 (6.0)	**<0.001**	3.1 (22.7)	2.8 (10.4)	1.1 (8.1)	**0.002**
Days Between Follow-Up PCL and Session 8 M (SD)	0.2 (5.8)	-1.9 (13.7)	0.3 (5.8)	**<0.001**	0.2 (7.0)	-0.4 (7.3)	0.2 (6.4)	0.230
Fiscal years 2008-2009	5.3 (16)	7.7 (42)	5.7 (68)	0.220	6.3 (16)	7.2 (42)	6.1 (68)	0.678
Fiscal years 2010-2011	37.3 (113)	35.5 (195)	39.4 (473)	0.284	36.3 (113)	36.1 (195)	39.1 (473)	0.468
Fiscal years 2012-2013	57.4 (174)	56.8 (312)	54.9 (659)	0.625	57.4 (174)	56.6 (312)	54.9 (659)	0.683
Age, M (SD)	47.2 (14.6)	42.8 (14.7)	45.8 (15.5)	**<0.001**	46.3 (16.4)	16.3 (44.6)	45.4 (15.4)	0.326
Women, % (n)	9.6 (29)	14.6 (80)	14.5 (174)	0.070	13.6 (29)	14.4 (80)	14.3 (174)	0.963
Married, % (n)	68.6 (208)	60.3 (331)	62.4 (749)	0.050	68.1 (208)	61.8 (331)	62.5 (749)	0.252
White Non-Hispanic, % (n)	48.2 (146)	62.7 (344)	65.8 (789)	**<0.001**	55.3 (146)	62.0 (344)	63.8 (789)	0.053
OEF/OIF/OND Veteran, % (n)	46.9 (142)	55.2 (303)	49.0 (588)	0.024	48.8 (142)	49.0 (303)	50.2 (588)	0.877
Rural, % (n)	32.3 (98)	33.2 (182)	30.8 (369)	0.580	30.5 (98)	33.6 (182)	30.5 (369)	0.462
Combat Exposure, % (n)	28.7 (87)	27.0 (148)	26.6 (319)	0.757	30.2 (87)	25.7 (148)	27.0 (319)	0.466
Sexual Trauma while in Military, % (n)	9.2 (28)	12.4 (68)	15.1 (181)	0.020	12.8 (28)	12.3 (68)	14.8 (181)	0.358
VA Disability Level 70% or Greater, % (n)	65.3 (198)	62.7 (344)	57.8 (694)	0.023	62.1 (198)	61.8 (344)	58.5 (694)	0.337
Charleson Comorbidity Index 1 or greater, % (n)	15.8 (48)	10.2 (56)	12.4 (149)	0.056	14.8 (48)	11.1 (56)	11.9 (149)	0.355
Psychotic Disorders, % (n)	1.0 (3)	1.6 (9)	1.6 (19)	0.721	0.4 (3)	1.5 (9)	1.6 (19)	0.133
Bipolar Mood Disorders, % (n)	3.6 (11)	3.1 (17)	3.5 (42)	0.888	5.3 (11)	3.0 (17)	3.5 (42)	0.382
Depressive Mood Disorders, % (n)	68.3 (207)	71.6 (393)	71.3 (855)	0.555	68.6 (207)	72.1 (393)	71.5 (855)	0.610
Non-PTSD Anxiety Disorders, % (n)	43.6 (132)	41.3 (227)	40.2 (482)	0.550	42.1 (132)	40.1 (227)	40.0 (482)	0.833
Traumatic Brain Injury, % (n)	17.2 (52)	22.8 (125)	17.0 (204)	0.013	17.8 (52)	20.7 (125)	17.6 (204)	0.291
Alcohol Use Disorders, % (n)	28.4 (86)	27.0 (148)	25.8 (310)	0.643	24.8 (86)	27.9 (148)	25.8 (310)	0.594
Opioid Use Disorders, % (n)	2.3 (7)	2.0 (11)	2.0 (24)	0.940	1.6 (7)	2.0 (11)	2.0 (24)	0.901
Other Drug Use Disorders, % (n)	14.9 (45)	13.8 (76)	13.5 (162)	0.830	12.1 (45)	13.0 (76)	13.3 (162)	0.863
Adequate Trial of Evidence-Based Antidepressant for PTSD, % (n)	41.3 (125)	33.2 (182)	32.0 (384)	0.009	37.3 (125)	33.0 (182)	32.5 (384)	0.363
PTSD Outpatient Clinical Team Use (540 or 561), % (n)	84.5 (256)	71.2 (391)	68.3 (820)	**<0.001**	78.3 (256)	71.8 (391)	70.4 (820)	0.098
Outpatient Mental Health Visits, M (SD)	31.7 (16.3)	27.6 (14.2)	26.9 (14.4)	**<0.001**	29.0 (15.5)	27.7 (15.3)	27.3 (14.8)	0.228
Outpatient Substance Abuse Visits, M (SD)	5.3 (13.9)	3.8 (15.3)	4.1 (11.9)	0.256	3.6 (9.8)	3.9 (16.7)	4.1 (12.0)	0.804
Outpatient Primary Care Visits, M (SD)	3.8 (3.5)	3.1 (2.5)	3.2 (3.1)	**0.005**	3.3 (3.2)	3.2 (2.9)	3.2 (3.2)	0.752
Emergency Department Visit for Psychiatric Indication, % (n)	8.3 (25)	7.1 (39)	8.5 (102)	0.607	6.9 (25)	7.1 (39)	8.5 (102)	0.510
Acute Mental Health Inpatient Admission, % (n)	6.3 (19)	7.8 (43)	6.6 (79)	0.572	5.0 (19)	7.5 (43)	6.5 (79)	0.426
Residential PTSD Admission, % (n)	15.8 (48)	7.5 (41)	7.0 (84)	**<0.001**	9.8 (48)	8.2 (41)	7.6 (84)	0.432
Residential Substance Abuse Admission, % (n)	4.6 (14)	1.1 (6)	2.2 (26)	**0.004**	2.4 (14)	1.1 (6)	2.2 (26)	0.241
Primary Therapist Characteristics, where known								
Age, M (SD)	44.1 (12.3)	43.3 (11.0)	43.5 (10.9)	0.664	43.1 (14.3)	43.7 (12.9)	43.4 (12.6)	0.861
Women, % (n)	44.2 (134)	60.5 (332)	55.0 (660)	**<0.001**	64.7 (134)	68.5 (332)	68.5 (660)	0.540
Psychologist, % (n)	65.7 (199)	67.8 (372)	64.0 (768)	0.327	69.9 (199)	66.5 (372)	65.2 (768)	0.395
Social Worker, % (n)	24.1 (73)	27.0 (148)	30.6 (367)	0.046	25.2 (73)	28.0 (148)	29.5 (367)	0.410
Nurse, % (n)	0.3 (1)	1.1 (6)	1.6 (19)	0.199	0.2 (1)	1.3 (6)	1.5 (19)	0.102
Psychiatrist, % (n)	0.7 (2)	1.1 (6)	0.8 (9)	0.720	0.7 (2)	1.2 (6)	0.8 (9)	0.683
Other, % (n)	9.2 (28)	3.1 (17)	2.9 (35)	**<0.001**	4.1 (28)	3.0 (17)	3.0 (35)	0.510
Prescribing Privileges, % (n)	5.6 (17)	7.8 (43)	7.9 (95)	0.379	6.5 (17)	7.7 (43)	7.7 (95)	0.813
Percentage of time in PTSD Service, M (SD)	72.0 (33.7)	57.5 (38.0)	55.2 (39.2)	**<0.001**	63.8 (45.6)	58.7 (41.2)	57.9 (38.5)	0.111
Percentage of time in Substance Abuse Service, M (SD)	3.4 (13.2)	3.2 (10.7)	3.7 (13.5)	0.736	2.6 (9.5)	3.0 (12.0)	3.5 (12.3)	0.338
Percentage of time in PTSD-Substance Abuse Service, M (SD)	1.1 (6.3)	1.0 (6.5)	0.8 (5.4)	0.505	0.8 (4.0)	0.8 (5.6)	0.8 (6)	0.973
Percentage of time in General Mental Health Service, M (SD)	17.5 (27.8)	29.1 (33.8)	31.2 (35.3)	**<0.001**	24.8 (41.4)	28.6 (35.9)	29.2 (34.0)	0.245
Percentage of time in Integrated Care Service, M (SD)	3.5 (12.6)	5.8 (17.4)	5.3 (16.2)	0.120	4.5 (17.5)	5.5 (17.2)	5.0 (15.8)	0.735

Note. PTSD=Posttraumatic Stress Disorder, PCL=PTSD Checklist, 8=eight sessions of evidence-based psychotherapy (EBP), 8 ST=eight sessions of EBP with the same the same psychotherapist, 8 14W S=eight sessions with the same therapist within 14 weeks, OEF/OIF/OND=Operations Enduring Freedom/Iraqi Freedom/New Dawn