Comparing Medications for *DSM-5* PTSD in Routine VA Practice

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ABSTRACT

Objective: Fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine have previously shown efficacy for posttraumatic stress disorder (PTSD). One prior study using US Department of Veterans Affairs (VA) medical records data to compare these agents found no differences in symptom reduction in clinical practice. The current study addresses 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including limited standardization of treatment duration, inability to account for prior treatment receipt, use of an outdated symptomatic assessment for PTSD, and lack of functional outcome.

Methods: A total of 834 VA outpatients were identified with *DSM-5* clinical diagnoses of PTSD between October 2016 and March 2018 who initiated one of the medications and met prespecified criteria for treatment duration and dose, combined with baseline and endpoint *DSM-5* PTSD Checklist (PCL-5) measurements. Twelve-week acute-phase changes in PCL-5 score and remission of PTSD symptoms were compared among patients receiving the different medications, as was use of acute psychiatric services 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 ($P = .008$ vs fluoxetine and $P < .0001$ vs paroxetine, sertraline, and topiramate). 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; $P = .03$).

Conclusions: There may be an advantage to venlafaxine over other agents in achieving acute-phase remission for *DSM-5* PTSD in routine clinical practice, but this finding 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.

J Clin Psychiatry 2020;81(6):20m13244

To cite: Shiner B, Leonard CE, Gui J, et al. Comparing medications for *DSM-5* PTSD in routine VA practice. *J Clin Psychiatry*. 2020;81(6):20m13244.

To share: https://doi.org/10.4088/JCP.20m13244

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Posttraumatic stress disorder (PTSD) is a serious condition that can follow exposure to a traumatic event; it is 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 US 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 are limited data comparing medications that are individually superior to placebo to one another in a single population, one prior VA study[6] used electronic medical record (EMR) data from 2008 to 2013 to compare the real-world clinical effectiveness of 5 efficacious medications. 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 edition 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 5 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 edition 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

Clinical Points

- Five medications for posttraumatic stress disorder (PTSD) with consistent efficacy in meta-analyses of randomized controlled trials—fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine—are also effective in routine clinical practice.
- Venlafaxine may have superior effects in helping patients achieve acute-phase (12-week) remission, but this finding 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.

6-month continuation phase among the 5 agents. This replication and extension study 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]

METHODS

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 October 1, 2016 to March 7, 2018. Although *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 October 1, 2016 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 daily doses, which were required for only the final 8 weeks 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 in the next subsection).

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 1 avoidance symptom, 2 negative alterations symptoms, and 2 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[13] used a severity score of ≤ 18 as a cutoff for remission. 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 subscores for PTSD symptom clusters as well as sleep difficulties using the sum of 2 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 department for a primary psychiatric indication during the 6-month continuation phase, which followed the initial 12-week acute phase.

Independent Variables

We measured 6 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-5 measurement differed from AMTs initiated without aligned PCL-5 measurement from October 1, 2016, to March 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 5 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 5 medications and the independent variables are an antiparsimonious specification of variables that have a plausible correlation with the outcome

Table 1. Explanation of Covariates

Variable	Description
Trial characteristics	
No. of adequate medication trials (AMTs) aligned with PCL-5 measurement	Adequate trials of fluoxetine, paroxetine, sertraline, topiramate, or venlafaxine aligned with PCL-5 measurement that each patient contributed to the outcomes analysis. Trials of different agents could overlap or dovetail, but we required a 1-year gap in prescriptions to count as a new trial of the same agent
PCL-5 severity measurement and timing	Baseline PCL-5 score, number of days between first available PTSD diagnosis and baseline PCL-5 measurement, number of days from baseline PCL-5 measurement to follow-up PCL-5 measurement for each trial included in the outcomes analysis
No. of prior AMTs	AMTs with or without PCL-5 measurement between 1999 and the start of each trial included in the outcomes analysis.
No. of prior adequate PE or CPT trials[a]	Episodes in which patients received ≥ 8 sessions of PE or CPT over the course of 1 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-5 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 a 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
Sex	Categorical male or female
Professional background	Eg, psychiatrist or nurse practitioner
Percentage of time spent seeing PTSD patients in various settings	Eg, 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-5 measurement
Outpatient visits	Eg, visits to specialized PTSD clinics or to primary care clinics
Acute psychiatric care use	Eg, emergency department visits for psychiatric indications or psychiatric hospitalizations
Residential treatment	Eg, stays in residential PTSD or substance abuse programs
Psychiatric comorbidities	Psychiatric diagnoses in the 2 years preceding the baseline PCL-5 measurement

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

Abbreviations: AMT = adequate medication trial, CPT = cognitive processing therapy, PCL-5 = *DSM-5* PTSD Checklist, PE = prolonged exposure, PTSD = posttraumatic stress disorder, VA = US Department of Veterans Affairs.

(ie, our 6 groups of covariates).[16,17] Using these propensity scores, we weighted participants to balance the covariate distributions across medications.

We compared continuous and categorical outcomes among the 5 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 $P < .01$ level after TWANG weighting. In balancing over 50 covariates, a Bonferroni correction would indicate a corrected α of $P < .001$. However, we conservatively maintained an α threshold of $P < .01$ for significant differences to avoid type II error. For acute-phase continuous outcomes of pre-post change in total PCL-5 score and subscores, we used linear regression analysis, whereby the coefficient of the variable tests the hypothesis that each of the 5 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

Table 2. Characteristics of New Trials of Evidence-Based Medications for PTSD at Adequate Dose and Duration, With Aligned PCL-5 Measurement, That Included Start Dates From October 1, 2016, Through March 7, 2018[a]

Characteristic	Value
No. of AMTs aligned with PCL-5 measurement	
1	94.2 (786)
2	5.8 (48)
No. of prior AMTs since October 1, 1999 (with or without PCL-5)	
0	81.1 (676)
1	15.0 (125)
2+	4.0 (33)
No. of prior adequate PE or CPT trials since October 1, 1999 (with or without PCL-5)	
0	93.2 (777)
1	6.2 (52)
2+	0.6 (5)
PCL-5 measurement relative to AMT, mean (SD)	
Days from first available PTSD diagnosis to baseline PCL-5	1,074.6 (1,378.7)
Days from baseline PCL-5 to follow-up PCL-5	80.8 (10.3)
Baseline PCL-5 score	57.8 (11.1)

[a]Values shown as % (number) unless otherwise noted.

Abbreviations: AMT = adequate medication trial (12 or more weeks of fluoxetine, sertraline, topiramate, paroxetine, or venlafaxine at required dose at a minimally adequate dose), CPT = cognitive processing therapy, FY = fiscal year, PCL = *DSM-5* PTSD Checklist, PTSD = posttraumatic stress disorder, PE = prolonged exposure.

of the variable tests the hypothesis that each of the 5 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 hazards 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 Inc), and developed causal models in R version 3.5.0 (R core team). These 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-5 measurement and 38,089 AMTs that were not aligned with PCL-5 measurement. Patients who had AMTs aligned with PCL-5 measurement generally contributed only 1 trial (Table 2), had received few prior adequate trials of evidence-based treatments for PTSD, and had severe baseline PTSD symptoms (mean [SD] PCL-5 score = 57.8 [11.1]). Inclusion of data from the early implementation of the EMR-based PCL-5 tool (October 1, 2014, to September 30, 2015) would have yielded a maximum of 21 additional AMTs aligned with PCL-5 measurement while making the analytic cohort less representative of the overall population receiving AMTs during the period of examination. There were 16 cases in which AMTs aligned with PCL-5 measurement overlapped, and all of these cases involved concurrent prescribing of topiramate with 1 of the 4 antidepressants. AMTs associated with PCL-5 measurement in our analytic cohort differed from contemporaneous AMTs without PCL-5 measurement in many ways (Table 3). Most notably, AMTs with measurement coincided with higher levels of all forms of individual and group psychotherapy, including prolonged exposure, individual cognitive processing therapy, and group cognitive processing therapy.

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 PCL-5 administered a mean (SD) of 1.1 (6.4) days after the start of the medication and endpoint PCL-5 administered a mean (SD) of 80.8 (10.3) days later. Mean (SD) baseline PCL-5 scores indicated a high burden of symptoms, ranging tightly from 57.5 (10.9) for the sertraline group to 58.6 (11.8) for the venlafaxine group.

All 5 of the medications were associated with moderate acute-phase improvements in PTSD symptoms (Table 4). The mean improvement in total PCL-5 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-5 change between the agents, there was a significant overall difference in achievement of remission ($P < .0001$). Pairwise comparisons indicated superior achievement of remission between the venlafaxine group compared to other groups (venlafaxine versus fluoxetine $P = .008$, venlafaxine versus paroxetine, sertraline, and topiramate $P < .0001$). 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 of remission in the 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 ($P < .0001$). Finally, sertraline was significantly superior to topiramate in achievement of acute-phase remission ($P < .0001$; 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 6-month continuation phase, there were 57 events. We added a time-varying covariate for whether patients stayed on their medication in the continuation phase and controlled for change in total PCL-5 score 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 (hazard ratio = 0.55; $P = .03$).

DISCUSSION

We compared the effectiveness of 5 evidence-based medications for *DSM-5* PTSD and found that they all appear

Table 3. Comparison of New Trials of Evidence-Based Medications for PTSD at Adequate Dose and Duration, With and Without Aligned PCL-5 Measurement, That Included Start Dates From October 1, 2016, Through March 7, 2018[a]

Variable	Trials Without PCL-5 Measurement (38,089)	Trials With PCL-5 Measurement (834)
Concurrent Treatment		
Any PE***	0.8 (319)	8.2 (68)
Sessions of PE, mean (SD)*	3.6 (2.8)	4.5 (3.1)
Any individual CPT***	2.7 (1,018)	29.6 (247)
Sessions of individual CPT, mean (SD)***	3.6 (2.9)	5.2 (3.3)
Any group CPT***	1.1 (421)	8.4 (70)
Sessions of group CPT, mean (SD)*	4.6 (4.3)	5.8 (4.2)
Any non-PE/CPT individual therapy***	32.2 (12,264)	62.2 (519)
Any non-CPT group therapy***	15.2 (5,792)	30.9 (258)
Any non-F/S/P/V antidepressant*	51.8 (19,749)	56.0 (467)
Any non-topiramate anticonvulsant	28.7 (10,924)	27.2 (227)
Any sedative-hypnotic***	21.9 (8,334)	16.1 (134)
Any opioid***	13.5 (5,149)	9.0 (75)
Any atypical antipsychotic	16.8 (6,380)	15.2 (127)
Any prazosin***	29.3 (11,143)	40.5 (338)
Any naltrexone or acamprosate**	2.9 (1,097)	4.8 (40)
Any opioid replacement therapy	1.3 (483)	1.3 (11)
Primary Prescribing Clinician Characteristics		
Age, mean (SD), y**	51.0 (12.1)	49.6 (12.3)
Women	37.9 (14,449)	37.1 (309)
Psychiatrist*	40.9 (15,588)	45.2 (377)
Other physician***	31.8 (12,103)	22.2 (185)
Physician assistant	4.3 (1,651)	4.9 (41)
Nurse practitioner	18.0 (6,858)	18.6 (155)
Pharmacist***	2.9 (1,120)	8.6 (72)
Percentage of time seeing PTSD patients in various settings		
PTSD service section (PCT or residential), mean (SD)***	5.7 (19.7)	9.4 (24.1)
Substance abuse service section, mean (SD)	2.5 (11.4)	2.1 (9.0)
General mental health service section, mean (SD)***	76.7 (39.7)	82.7 (34.3)
Integrated care service section, mean (SD)***	5.6 (17.3)	8.1 (21.1)
Primary care service section, mean (SD)***	18.3 (37.3)	12.0 (31.1)
Patient Characteristics at Baseline		
Age, mean (SD), y***	46.5 (14.6)	40.9 (11.1)
Women	16.9 (6,434)	16.1 (134)
Married	54.9 (20,925)	55.8 (465)
Rural	33.6 (12,789)	33.0 (275)
White non-Hispanic	63.2 (24,079)	60.8 (507)
Black non-Hispanic	20.6 (7,835)	18.1 (151)
Hispanic***	9.2 (3,491)	13.3 (111)
OEF/OIF/OND veteran***	48.7 (18,533)	68.9 (575)
Vietnam veteran***	11.9 (4,535)	4.0 (33)
Combat exposure***	42.2 (16,069)	49.9 (416)
Sexual trauma while in military	14.9 (5,688)	15.1 (126)
VA disability level 70% or greater	49.7 (18,933)	50.8 (424)
Service Use Characteristics in the 1 Year Preceding Baseline		
Any PTSD outpatient clinical team visits***	19.1 (7,260)	33.7 (281)
No. of PTSD outpatient clinical team visits, mean (SD)	9.6 (15.7)	9.6 (11.2)
Any outpatient mental health visits	88.2 (33,612)	88.1 (735)
No. of outpatient mental health visits, mean (SD)***	20.6 (42.1)	26.9 (45.5)
Any outpatient substance abuse visits***	11.0 (4,205)	15.3 (128)
No. of outpatient substance abuse visits, mean (SD)	22.9 (37.7)	21.9 (42.7)
Any outpatient primary care visits***	87.9 (33,495)	82.1 (685)
No. of outpatient primary care visits, mean (SD)***	7.1 (7.8)	6.0 (5.9)
Any ED visits for psychiatric indication	13.1 (4,979)	13.2 (110)
No. of ED visits for psychiatric indication, mean (SD)	2.1 (2.2)	1.8 (1.6)
Any acute inpatient mental health treatment**	8.6 (3,257)	11.3 (94)
Days of acute inpatient mental health, mean (SD)	16.1 (24.8)	17.8 (23.3)
Any residential PTSD treatment***	1.0 (364)	2.9 (24)
Days of residential PTSD treatment, mean (SD)	44.8 (40.7)	28.8 (21.0)
Any residential substance abuse treatment	1.9 (728)	2.5 (21)
Days of residential substance abuse treatment, mean (SD)	43.2 (43.3)	39.3 (33.6)
Any integrated care visits***	26.5 (10,110)	35.3 (294)
Days of integrated care visits, mean (SD)	3.9 (7.9)	3.1 (4.3)
Any neurology visits	12.1 (4,596)	10.1 (84)
Days of neurology visits, mean (SD)	2.4 (2.3)	2.3 (1.8)

(continued)

Table 3 (continued).

Variable	Trials Without PCL-5 Measurement (38,089)	Trials With PCL-5 Measurement (834)
Any sleep clinic visits	14.7 (5,597)	14.6 (122)
Days of sleep clinic visits, mean (SD)	2.2 (1.6)	2.3 (1.8)
Any polytrauma TBI specialty clinic visits***	6.3 (2,379)	11.5 (96)
Days of polytrauma TBI specialty clinic visits, mean (SD)	4.7 (13.7)	3.3 (4.7)
Comorbidities in the 2 Years Preceding Baseline		
Pain disorder	80.7 (30,749)	80.9 (675)
Headache disorder***	31.4 (11,974)	36.9 (308)
Psychotic disorders***	3.8 (1,449)	1.6 (13)
Bipolar mood disorders*	8.1 (3,103)	6.0 (50)
Depressive mood disorders***	73.0 (27,802)	80.8 (674)
Anxiety disorders	46.8 (17,840)	50.0 (417)
Traumatic brain injury***	8.6 (3,267)	14.7 (123)
Alcohol use disorders***	27.6 (10,522)	33.3 (278)
Opioid use disorders*	5.7 (2,176)	7.3 (61)
Other substance use disorders***	16.6 (6,337)	21.0 (175)

[a]Values shown as % (number) unless otherwise noted.
*$P < .05$.
**$P < .01$.
***$P < .001$.
Abbreviations: CPT = cognitive processing therapy, F/S/P/V = fluoxetine/sertraline/paroxetine/venlafaxine, FY = fiscal year, OEF/OIF/OND = Operations Enduring Freedom/Iraqi Freedom/New Dawn, VA = US Department of Veterans Affairs, PCL-5 = *DSM-5* PTSD Checklist, PCT = PTSD care team, PE = prolonged exposure, PTSD = posttraumatic stress disorder, TBI = traumatic brain injury.

Table 4. Weighted Outcomes for Patients With an Adequate Trial of an Effective Medication for PTSD Plus PCL-5 Measurement[a]

Agent	Fluoxetine (F) (n = 228)	Paroxetine (P) (n = 87)	Sertraline (S) (n = 307)	Topiramate (T) (n = 96)	Venlafaxine (V) (n = 116)	Pairwise Differences*
Overall Outcomes						
Baseline PCL-5 score	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-5 score	−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	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	−1.8 (4.2)	−1.6 (4.9)	−1.8 (3.6)	−1.8 (4.5)	−2.1 (5.2)	No differences
Baseline avoidance	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	−1.1 (2.4)	−0.8 (2.2)	−0.7 (1.8)	−0.7 (2.9)	−1.0 (2.6)	No differences
Baseline NACM	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	−2.8 (6.2)	−2.4 (6.2)	−2.5 (5.1)	−2.2 (5.5)	−4.2 (7.6)	No differences
Baseline hyperarousal	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	−2.5 (5.2)	−2.1 (5.6)	−2.5 (4.0)	−2.1 (5.1)	−2.8 (6.2)	No differences
Baseline sleep	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	−0.7 (2.1)	−0.8 (2.3)	−1.1 (1.8)	−0.9 (2.3)	−0.9 (2.7)	No differences

[a]Values shown as mean (SD) unless otherwise noted.
*Significant differences are assessed at $P < .05$ for the omnibus comparison, with pairwise testing when indicated.
Abbreviations: NACM = negative alterations in cognitions and mood, *DSM-5* PCL-5 = PTSD Checklist, PTSD = posttraumatic stress disorder.

to be effective in routine clinical practice. Furthermore, we found evidence of possible superiority of venlafaxine in achieving acute-phase remission. Although 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 5 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[6] comparing these 5 agents in routine practice, and these changes may have accounted for the differences in findings. First, 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 [SD] length of 254.1 [119.5] days), we standardized the trial length and

achieved a treatment duration that better approximated the typical acute-phase clinical trial (mean [SD] length of 80.8 [10.3] days). Thus, we have substantially 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 of 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, the recent 4-site VA and private sector study by Rauch et al[21] of PTSD treatment approaches for Iraq and Afghanistan veterans included a sertraline-plus–enhanced medication management arm. Enhanced medication management consisted of 8 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 in 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-5–based inclusion criteria for our analytic cohort differed significantly from those receiving adequate medication trials without PCL-5 measurement in several ways. Most notably, those with aligned PCL-5 measurement received far more psychotherapy. The limited availability of PCL-5 data indicates low use of measurement-based care in routine psychopharmacology practice, despite a VA initiative to promote measurement-based care 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 eye movement desensitization and reprocessing. 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. Last, we considered only 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 in 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.

Submitted: January 9, 2020; accepted May 18, 2020.

Published online: October 13, 2020.

Potential conflicts of interest: None.

Funding/support: This study was funded by the Department of Defense Peer Reviewed Medical Research Program (PR160203), Congressionally Directed Medical Research Program, Fort Dietrich, Maryland (Dr Shiner), as well as a Department of Veterans Affairs Health Services Research and Development Career Development Award (CDA11-263), VA Office of Research and Development, Washington, DC (Dr Shiner).

Role of the sponsor: The sponsors did not have any role in the study design, methods, analysis, and interpretation of results or in preparation of the manuscript and the decision to submit it for publication.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily represent the position or policy of the US Department of Veterans Affairs or US Department of Defense.

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/.

Supplementary material: Available at PSYCHIATRIST.COM.

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THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Comparing Medications for *DSM-5* PTSD in Routine VA Practice

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DOI Number: https://doi.org/10.4088/JCP.20m13244

List of Supplementary Material for the article

1. Table 1 — Participants with an Adequate Trial of an Effective Medication for PTSD plus Outcomes Measurement, including start dates from October 1, 2016 through March 7, 2018 (Unweighted)
2. Table 2 — Participants with an Adequate Trial of an Effective Medication for PTSD plus Outcomes Measurement, including start dates from October 1, 2016 through March 7, 2018 (Weighted)

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Table 1: Participants with an Adequate Trial of an Effective Medication for PTSD plus Outcomes Measurement, including start dates from October 1, 2016 through March 7, 2018 (Unweighted)

Agent	Fluoxetine (n=228)	Paroxetine (n=87)	Sertraline (n=307)	Topiramate (n=96)	Venlafaxine (n=116)	Pairwise Differences
Trial Characteristics						
Number of Prior Adequate EBM Trials, M(SD)	1.1 (0.2)	1.0 (0.2)	1.0 (0.2)	1.2 (0.4)	1.1 (0.2)	PTV≠S
Number of Prior Adequate EBP Trials, M(SD)	0.1 (0.3)	0.1 (0.3)	0.0 (0.2)	0.1 (0.4)	0.1 (0.3)	No differences
Days from First PTSD Diagnosis to Baseline PCL, M (SD)	1139 (1390)	1095 (1350)	919 (1293)	1392 (1621)	1081 (1348)	No differences
Days from Baseline PCL to Follow-Up PCL, M (SD)	79.5 (9.7)	80.9 (10.2)	81.8 (11.2)	80.0 (10.2)	81.3 (8.9)	No differences
Concurrent Treatment						
Sessions of PE, M, SD	5.5 (3.5)	3.3 (3.2)	3.5 (2.4)	5.0 (2.8)	4.9 (3.4)	No differences
Sessions of Individual CPT, M, SD	5.3 (3.3)	4.6 (3.2)	4.6 (3.2)	6.5 (3.0)	5.9 (3.6)	No differences
Sessions of Group CPT, M, SD	6.6 (5.2)	3.8 (2.9)	5.9 (4.0)	4.9 (4.7)	6.8 (3.1)	No differences
Any Non-PE/CPT Individual Therapy, %, n	64.9 (148)	51.7 (45)	61.6 (189)	57.3 (55)	70.7 (82)	P≠V
Any Non-CPT Group Therapy, %, n	31.1 (71)	19.5 (17)	24.8 (76)	45.8 (44)	43.1 (50)	TV≠P; TV≠S
Any Non-F/S/P/V Antidepressant, %, n	55.3 (126)	57.5 (50)	53.1 (163)	61.5 (59)	59.5 (69)	No differences
Any Non-Topiramate Anticonvulsant, %, n	27.2 (62)	26.4 (23)	23.1 (71)	32.3 (31)	34.5 (40)	No differences
Any Sedative/Hypnotics, %, n	15.8 (36)	17.2 (15)	13.7 (42)	15.6 (15)	22.4 (26)	No differences
Any Opioid, %, n	10.1 (23)	4.6 (4)	9.5 (29)	8.3 (8)	9.5 (11)	No differences
Any Atypical Antipsychotic, %, n	17.5 (40)	12.6 (11)	12.7 (39)	15.6 (15)	19.0 (22)	No differences
Any Prazosin, %, n	41.2 (94)	27.6 (24)	44.3 (136)	33.3 (32)	44.8 (52)	P≠S
Any Naltrexone or Acamprosate, %, n	6.1 (14)	2.3 (2)	3.9 (12)	5.2 (5)	6.0 (7)	No differences
Any Opioid Replacement Therapy, %, n	1.8 (4)	1.2 (1)	1.6 (5)	2.1 (2)	1.7 (2)	No differences
Primary Prescribing Clinician Characteristics						
Age, M (SD)	49.7 (12.0)	50.6 (10.3)	47.9 (12.8)	52.5 (12.3)	50.4 (12.1)	No differences
Women, % (n)	39.0 (89)	33.3 (29)	32.9 (101)	47.9 (46)	37.9 (44)	S≠T
Psychiatrist, % (n)	46.9 (107)	49.4 (43)	43.0 (132)	39.6 (38)	49.1 (57)	No differences
Other Physician, % (n)	18.4 (42)	18.4 (16)	24.8 (76)	37.5 (36)	12.9 (15)	FPV≠T; S≠V
Physician Assistant, % (n)	3.5 (8)	5.8 (5)	4.9 (15)	4.2 (4)	7.8 (9)	No differences
Nurse Practitioner, % (n)	20.6 (47)	21.8 (19)	16.9 (52)	15.6 (15)	19.0 (22)	No differences
Pharmacist, % (n)	9.2 (21)	4.6 (4)	10.1 (31)	3.1 (3)	11.2 (13)	No differences
Percentage of Time Seeing PTSD Patients in Various Settings						
PTSD Service Section (PCT or residential), M (SD)	11.0 (24.5)	11.7 (28.4)	9.2 (25.1)	5.4 (18.8)	8.2 (21.1)	No differences
Substance Abuse Service Section, M (SD)	1.9 (7.1)	1.2 (4.8)	2.2 (9.4)	3.0 (12.4)	2.6 (10.5)	No differences
PTSD and Substance Abuse Service Section, M (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	No differences
General Mental Health Service Section, M (SD)	87.1 (29.7)	79.9 (38.0)	84.2 (33.2)	63.4 (45.3)	88.2 (26.7)	FSPV≠T
Integrated Care Service Section, M (SD)	9.2 (23.4)	8.4 (21.8)	9.1 (21.8)	1.2 (6.8)	9.0 (21.1)	No differences
Primary Care Service Section, M (SD)	8.5 (27.2)	15.8 (35.1)	12.3 (31.4)	22.5 (39.9)	6.5 (22.9)	FV≠T
Patient Characteristics at Baseline						
Age, M (SD)	39.8 (10.9)	41.5 (11.6)	42.1 (11.7)	41.2 (9.7)	39.5 (10.8)	No differences
Women, % (n)	18.0 (41)	9.2 (8)	12.4 (38)	28.1 (27)	17.2 (20)	PS≠T
Married, % (n)	54.0 (123)	50.6 (44)	60.6 (186)	52.1 (50)	53.5 (62)	No differences
Rural, % (n)	32.0 (73)	27.6 (24)	36.5 (112)	31.3 (30)	31.0 (36)	No differences
White Non-Hispanic, % (n)	57.5 (131)	63.2 (55)	62.9 (193)	53.13 (51)	66.4 (77)	No differences
Black Non-Hispanic, % (n)	18.0 (41)	16.1 (14)	17.3 (53)	26.0 (25)	15.5 (18)	No differences
Hispanic, % (n)	17.1 (39)	9.2 (8)	12.1 (37)	13.5 (13)	12.1 (14)	No differences
OEF/OIF/OND Veteran, % (n)	67.1 (153)	77.0 (67)	68.7 (211)	67.7 (65)	68.1 (79)	No differences
Vietnam Veteran, % (n)	4.4 (10)	3.5 (3)	5.2 (16)	0.0 (0)	3.5 (4)	No differences
Combat Exposure, % (n)	48.3 (110)	58.6 (51)	49.8 (153)	47.9 (46)	48.3 (56)	No differences
Sexual Trauma while in Military, % (n)	17.5 (40)	11.5 (10)	10.7 (33)	28.1 (27)	13.8 (16)	PSV≠T
VA Disability Level 70% or Greater, % (n)	50.9 (116)	50.6 (44)	44.6 (137)	59.4 (57)	60.3 (70)	S≠V
Service Use Characteristics in the 1 Year Preceding Baseline						
Number of PTSD Outpatient Clinical Team Visits, M (SD)	11.5 (12.5)	5.3 (6.0)	7.3 (8.5)	12.7 (12.9)	10.7 (12.6)	No differences
Number of Outpatient Mental Health Visits, M (SD)	27.4 (40.6)	19.7 (26.7)	20.9 (44.0)	43.0 (69.8)	35.3 (44.4)	S≠T
Number of Outpatient Substance Abuse Visits, M (SD)	20.8 (26.1)	15.6 (22.0)	22.5 (49.4)	36.5 (73.1)	15.0 (26.3)	No differences
Number of Outpatient Primary Care Visits, M (SD)	5.9 (5.1)	7.5 (9.7)	5.2 (5.2)	6.7 (6.1)	6.4 (5.4)	No differences
Number of ED Visit for Psychiatric Indication, M (SD)	2.2 (1.7)	1.8 (1.4)	2.2 (2.5)	2.5 (3.4)	2.9 (2.6)	No differences
Days of Acute Inpatient Mental Health, M (SD)	19.1 (30.3)	18.8 (13.8)	9.8 (9.1)	30.3 (28.8)	22.0 (27.2)	No differences
Days Residential PTSD Treatment, M (SD)	27.6 (24.1)	0.0 (0.0)	31.6 (23.7)	28.0 (17.4)	25.5 (19.9)	No differences
Days Residential Substance Abuse Treatment, M (SD)	43.6 (41.0)	54.0 (0.0)	29.2 (13.5)	39.4 (43.8)	41.3 (40.5)	No differences
Days Integrated Care Visits, M (SD)	3.6 (6.5)	3.5 (4.1)	2.5 (2.8)	2.4 (1.8)	3.8 (3.1)	No differences
Days Neurology Visits, M (SD)	1.9 (1.5)	2.3 (1.9)	2.3 (1.6)	2.9 (2.4)	1.6 (1.0)	No differences
Days Sleep Clinic Visits, M (SD)	2.6 (2.0)	3.5 (3.6)	2.0 (1.3)	2.4 (1.7)	2.0 (1.1)	No differences
Days Polytrauma TBI Specialty Clinic Visits, M (SD)	2.6 (2.7)	3.4 (2.9)	1.6 (1.3)	6.4 (9.4)	4.5 (4.9)	No differences
Comorbidities in the 2 Years Preceding Baseline						
Pain Disorder, % (n)	77.6 (177)	77.0 (67)	80.1 (246)	89.6 (86)	85.3 (99)	No differences
Headache Disorder, % (n)	33.3 (76)	34.5 (30)	30.6 (94)	69.8 (67)	35.3 (41)	FPSV≠T

Psychotic Disorders, % (n)	2.2 (5)	1.2 (1)	1.3 (4)	1.0 (1)	1.7 (2)	No differences
Bipolar Mood Disorders, % (n)	4.8 (11)	9.2 (8)	5.2 (16)	8.3 (8)	6.0 (7)	No differences
Depressive Mood Disorders, % (n)	81.1 (185)	72.4 (63)	80.5 (247)	83.3 (80)	85.3 (99)	No differences
Anxiety Disorders, %(n)	47.8 (109)	46.0 (40)	52.4 (161)	52.1 (50)	49.1 (57)	No differences
Traumatic Brain Injury, % (n)	14.5 (33)	13.8 (12)	12.1 (37)	20.8 (20)	18.1 (21)	No differences
Alcohol Use Disorders, % (n)	33.3 (76)	34.5 (30)	27.7 (85)	38.5 (37)	43.1 (50)	S≠V
Opioid Use Disorders, % (n)	7.9 (18)	4.6 (4)	5.2 (16)	11.5 (11)	10.3 (12)	No differences
Other Substance Use Disorders, % (n)	22.8 (52)	20.7 (18)	15.6 (48)	27.1 (26)	26.7 (31)	S≠V

*Significant Differences are assessed at p<0.01 for the Omnibus comparison, with pair-wise testing where indicated.

Abbreviations. PTSD=posttraumatic stress disorder, PCL=PTSD Checklist, FY=Fiscal Year, EBM=Evidence-Based Medication for PTSD, EBP=Evidence-Based Psychotherapy for PTSD, 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

Supplementary Table 2: Participants with an Adequate Trial of an Effective Medication for PTSD plus Outcomes Measurement, including start dates from October 1, 2016 through March 7, 2018 (Weighted)

Agent	Fluoxetine (n=228)	Paroxetine (n=87)	Sertraline (n=307)	Topiramate (n=96)	Venlafaxine (n=116)	Pairwise Differences
Trial Characteristics						
Number of Prior Adequate EBM Trials, M(SD)	0.3 (0.6)	0.3 (0.5)	0.2 (0.5)	0.4 (1.1)	0.2 (0.5)	No differences
Number of Prior Adequate EBP Trials, M(SD)	0.1 (0.3)	0.1 (0.2)	0.1 (0.2)	0.1 (0.3)	0.1 (0.3)	No differences
Days from First PTSD Diagnosis to Baseline PCL, M (SD)	1115 (1381)	969 (1379)	991 (1413)	1251 (2037)	1089 (1351)	No differences
Days from Baseline PCL to Follow-Up PCL, M (SD)	79.8 (10.3)	80.8 (11.0)	81.1 (10.8)	79.0 (22.0)	80.8 (11.0)	No differences
Concurrent Treatment						
Sessions of PE, M, SD	0.5 (1.9)	0.1 (1.0)	0.3 (1.2)	0.4 (1.6)	0.4 (1.7)	No differences
Sessions of Individual CPT, M, SD	1.6 (3.0)	1.2 (3.0)	1.4 (3.1)	1.6 (3.7)	1.6 (3.4)	No differences
Sessions of Group CPT, M, SD	0.5 (2.2)	0.4 (1.5)	0.3 (2.1)	0.3 (1.4)	0.5 (1.5)	No differences
Any Non-PE/CPT Individual Therapy, %, n	64.2 (148)	53.7 (45)	63.6 (189)	55.8 (55)	69.3 (82)	No differences
Any Non-CPT Group Therapy, %, n	30.2 (71)	22.5 (17)	27.7 (76)	37.2 (44)	34.3 (50)	No differences
Any Non-F/S/P/V Antidepressant, %, n	54.6 (126)	60.0 (50)	54.9 (163)	67.9 (59)	59.5 (69)	No differences
Any Non-Topiramate Anticonvulsant, %, n	27.5 (62)	24.9 (23)	25.0 (71)	33.3 (31)	33.5 (40)	No differences
Any Sedative/Hypnotics, %, n	15.4 (36)	16.9 (15)	14.9 (42)	17.4 (15)	18.0 (26)	No differences
Any Opioid, %, n	10.2 (23)	3.6 (4)	10.4 (29)	8.1 (8)	9.6 (11)	No differences
Any Atypical Antipsychotic, %, n	18.1 (40)	11.7 (11)	14.5 (39)	19.8 (15)	15.4 (22)	No differences
Any Prazosin, %, n	41.8 (94)	30.6 (24)	41.9 (136)	31.6 (32)	45.2 (52)	No differences
Any Naltrexone or Acamprosate, %, n	6.6 (14)	1.6 (2)	4.7 (12)	4.1 (5)	3.8 (7)	No differences
Any Opioid Replacement Therapy, %, n	1.6 (4)	1.2 (1)	2.4 (5)	1.9 (2)	1.0 (2)	No differences
Primary Prescribing Clinician Characteristics						
Age, M (SD)	49.7 (13.9)	50.0 (13.3)	49.1 (14.5)	52.1 (16.8)	50.7 (15.0)	No differences
Women, % (n)	54.8 (89)	49.6 (29)	51.8 (101)	52.0 (46)	60.5 (44)	No differences
Psychiatrist, % (n)	45.1 (107)	48.5 (43)	44.7 (132)	46.3 (38)	51.3 (57)	No differences
Other Physician, % (n)	19.2 (42)	19.2 (16)	24.1 (76)	30.9 (36)	14.7 (15)	No differences
Physician Assistant, % (n)	4.0 (8)	6.8 (5)	4.9 (15)	2.8 (4)	5.6 (9)	No differences
Nurse Practitioner, % (n)	21.5 (47)	21.1 (19)	16.7 (52)	17.3 (15)	19.6 (22)	No differences
Pharmacist, % (n)	8.8 (21)	4.3 (4)	8.9 (31)	2.7 (3)	8.8 (13)	No differences
Percentage of Time Seeing PTSD Patients in Various Settings						
PTSD Service Section (PCT or residential), M (SD)	9.0 (21.2)	10.4 (25.6)	8.9 (24.4)	7.1 (25.5)	8.5 (25.4)	No differences
Substance Abuse Service Section, M (SD)	1.8 (7.7)	1.2 (4.4)	2.2 (9.3)	2.0 (9.1)	2.2 (8.3)	No differences
PTSD and Substance Abuse Service Section, M (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	No differences
General Mental Health Service Section, M (SD)	84.4 (36.7)	79.8 (40.3)	83.9 (34.4)	72.9 (54.3)	88.5 (29.1)	No differences
Integrated Care Service Section, M (SD)	8.2 (20.6)	6.9 (18.9)	7.8 (19.1)	1.6 (10.6)	8.3 (21.1)	F≠T
Primary Care Service Section, M (SD)	11.0 (34.4)	16.2 (38.8)	12.4 (32.6)	17.1 (46.0)	6.3 (25.5)	No differences
Patient Characteristics at Baseline						
Age, M (SD)	39.6 (10.8)	41.8 (12.0)	41.5 (11.4)	39.7 (10.6)	40.2 (13.1)	No differences
Women, % (n)	17.9 (41)	9.9 (8)	13.0 (38)	21.8 (27)	16.9 (20)	No differences
Married, % (n)	56.4 (123)	54.6 (44)	61.6 (186)	55.0 (50)	56.5 (62)	No differences
Rural, % (n)	34.8 (73)	26.9 (24)	38.1 (112)	37.3 (30)	34.0 (36)	No differences
White Non-Hispanic, % (n)	57.2 (131)	64.7 (55)	62.6 (193)	59.9 (51)	63.3 (77)	No differences
Black Non-Hispanic, % (n)	18.2 (41)	15.1 (14)	18.0 (53)	19.1 (25)	15.2 (18)	No differences
Hispanic, % (n)	17.4 (39)	8.7 (8)	11.9 (37)	12.9 (13)	14.2 (14)	No differences
OEF/OIF/OND Veteran, % (n)	67.3 (153)	76.1 (67)	69.8 (211)	72.2 (65)	65.9 (79)	No differences
Vietnam Veteran, % (n)	4.1 (10)	3.4 (3)	4.2 (16)	0.0 (0)	4.5 (4)	FSV≠T; STV≠P; S≠V
Combat Exposure, % (n)	47.9 (110)	54.3 (51)	51.0 (153)	56.2 (46)	49.3 (56)	No differences
Sexual Trauma while in Military, % (n)	17.3 (40)	10.9 (10)	11.1 (33)	21.1 (27)	12.9 (16)	No differences
VA Disability Level 70% or Greater, % (n)	51.8 (116)	50.2 (44)	46.2 (137)	55.7 (57)	52.7 (70)	No differences

Service Use Characteristics in the 1 Year Preceding Baseline						
Number of PTSD Outpatient Clinical Team Visits, M (SD)	3.4 (7.4)	1.6 (4.7)	2.6 (8.4)	4.1 (10.0)	3.1 (6.6)	No differences
Number of Outpatient Mental Health Visits, M (SD)	24.6 (41.3)	16.1 (24.6)	21.6 (48.5)	25.8 (39.8)	21.8 (32.0)	No differences
Number of Outpatient Substance Abuse Visits, M (SD)	3.0 (12.1)	2.4 (12.1)	3.1 (20.8)	4.4 (17.9)	1.7 (6.5)	No differences
Number of Outpatient Primary Care Visits, M (SD)	4.9 (5.0)	5.0 (7.5)	4.5 (5.6)	4.9 (6.8)	5.0 (7.1)	No differences
Number of ED Visit for Psychiatric Indication, M (SD)	0.6 (1.3)	0.5 (1.1)	0.7 (1.9)	0.5 (1.3)	0.7 (1.4)	No differences
Days of Acute Inpatient Mental Health, M (SD)	2.4 (12.2)	2.2 (6.5)	1.5 (6.4)	3.1 (11.6)	2.2 (7.2)	No differences
Days Residential PTSD Treatment, M (SD)	0.6 (4.8)	0.0 (0)	1.3 (9.5)	0.8 (5.1)	1.0 (6.2)	No differences
Days Residential Substance Abuse Treatment, M (SD)	1.5 (12.5)	0.9 (8.3)	0.5 (4.5)	1.2 (7.3)	0.6 (4.6)	No differences
Days Integrated Care Visits, M (SD)	1.4 (5.2)	1.0 (2.0)	1.0 (2.6)	0.5 (1.2)	0.9 (1.9)	No differences
Days Neurology Visits, M (SD)	0.2 (0.6)	0.2 (0.9)	0.2 (0.8)	0.4 (1.2)	0.2 (0.6)	No differences
Days Sleep Clinic Visits, M (SD)	0.4 (1.2)	0.3 (1.3)	0.2 (0.8)	0.3 (1.3)	0.3 (0.7)	No differences
Days Polytrauma TBI Specialty Clinic Visits, M (SD)	0.3 (1.3)	0.4 (1.3)	0.1 (0.7)	0.7 (3.0)	0.5 (1.8)	No differences
Comorbidities in the 2 Years Preceding Baseline						
Pain Disorder, % (n)	78.5 (177)	75.0 (67)	81.0 (246)	88.2 (86)	78.5 (99)	No differences
Headache Disorder, % (n)	33.1 (76)	33.9 (30)	32.1 (94)	52.9 (67)	40.3 (41)	No differences
Psychotic Disorders, % (n)	2.2 (5)	0.9 (1)	1.6 (4)	0.4 (1)	1.7 (2)	No differences
Bipolar Mood Disorders, % (n)	4.9 (11)	7.3 (8)	6.4 (16)	8.6 (8)	4.6 (7)	No differences
Depressive Mood Disorders, % (n)	81.1 (185)	74.8 (63)	81.3 (247)	81.3 (80)	86.3 (99)	No differences
Anxiety Disorders, %(n)	47.5 (109)	45.9 (40)	53.7 (161)	56.3 (50)	44.3 (57)	No differences
Traumatic Brain Injury, % (n)	13.8 (33)	13.7 (12)	11.8 (37)	25.1 (20)	16.5 (21)	No differences
Alcohol Use Disorders, % (n)	33.3 (76)	32.6 (30)	28.8 (85)	34.1 (37)	38.2 (50)	No differences
Opioid Use Disorders, % (n)	7.5 (18)	3.6 (4)	6.9 (16)	15.6 (11)	7.6 (12)	No differences
Other Substance Use Disorders, % (n)	22.1 (52)	19.3 (18)	17.8 (48)	27.0 (26)	23.2 (31)	No differences

*Significant Differences are assessed at p<0.01 for the Omnibus comparison, with pair-wise testing where indicated.
Abbreviations. PTSD=posttraumatic stress disorder, PCL=PTSD Checklist, FY=Fiscal Year, EBM=Evidence-Based Medication for PTSD, EBP=Evidence-Based Psychotherapy for PTSD, 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