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Large Posttraumatic Stress Disorder Improvement and Antidepressant Medication Adherence

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Author Statement

The views expressed in this report do not necessarily reflect those of the Veterans' Health Administration.

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All authors contributed to conception and design.

Jeffrey Scherrer and Joanne Salas contributed to data acquisition, analysis, and interpretation.

Jeffrey Scherrer and Joanne Salas drafted the manuscript.

All authors critically reviewed the manuscript for intellectual content and gave final approval.

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Abstract

Background: Patients with vs. without posttraumatic stress disorder (PTSD) are more likely to have poor antidepressant medication (ADM) adherence but it is unclear if improved PTSD is associated with ADM adherence. We determined if clinically meaningful PTSD symptom reduction was associated with ADM adherence.

Methods: Electronic health record data (2008-2015) was obtained from 742 Veterans Health Affairs (VHA) patients using PTSD specialty clinics with a PTSD diagnosis and PTSD checklist (PCL) score ≥50. The last PCL in the exposure year after the first PCL≥50 was used to identify patients with a clinically meaningful PCL decrease (≥20 point) versus those without (< 20 point). Patients had a depression diagnosis in the 12-months before the exposure year and received an ADM in the exposure year. Proportion of days covered ≥80% in exposure year defined adherence. Confounding was controlled using propensity scores and inverse probability of treatment weighting.

Results: Patients were 42.2±13.1 years of age, 63.9% white and 18.9% had a clinically meaningful PCL decrease. After controlling for confounding variables, patients with vs. without a clinically meaningful PCL decrease were significantly more likely to be adherent (OR= 1.78; 95% CI: 1.16-2.73). However, adherence remained low in both patients with and without meaningful PCL decrease (53.5% vs. 39.3%).

Limitations.—The sample was limited to VHA patients. Patients may not have taken medication as prescribed.

Conclusions: Large reductions in PTSD symptoms are associated with ADM adherence. Prior literature suggests ADM adherence improves depression symptoms. Thus, PTSD symptom reduction may lead to better depression outcomes.

Keywords

PTSD symptoms; depression; antidepressant medication adherence

INTRODUCTION

Patients with vs. without posttraumatic stress disorder (PTSD) are significantly more likely to report not taking medications as prescribed, forgetting to take medicines and skipping doses (Kronish et al., 2012). Patients with anxiety disorders are less adherent to antidepressant medications (ADM) (Stein et al., 2006) and a majority of patients with PTSD are non-adherent to ADMs in the 12-months following residential treatment (Lockwood et al., 2009). Yet, the evidence is inconsistent. A large retrospective cohort study of patients with depression discharged on ADMs found those with vs. without comorbid PTSD were more often ADM adherent (Zivin et al., 2009).

While the majority of existing studies support the conclusion that PTSD is associated with poor ADM adherence, to our knowledge, there is no literature on whether large PTSD improvement is associated with greater likelihood of ADM adherence. Several studies have found ADM adherence is a strong predictor of depression improvement (Akerblad et al., 2006; Ho et al., 2016; Stein et al., 2006). Among patients beginning ADM therapy, response to treatment by 24 weeks is markedly higher in adherent vs. non-adherent patients (82.5% vs. 55.8%) (Akerblad et al., 2006). If patients who have a clinically meaningful PTSD symptom decrease are more likely to be ADM adherent compared to patients with no or less than clinically meaningful improvement, the success of pharmacotherapy for depression may be enhanced by first targeting reductions in PTSD severity. Approximately 50% of people with PTSD also have a diagnosis of major depressive disorder (Flory and Yehuda, 2015), and PTSD and depressive symptoms change similarly over time such that comorbid depression improves in tandem with PTSD (Norman et al., 2011). The current study used a retrospective cohort of Veterans Health Affairs (VHA) patients with PTSD to determine if patients who experience a ≥20 point PTSD Checklist (PCL) score decrease compared to <20 point PCL score decrease are more likely to be ADM adherent.

METHODS

A retrospective cohort study was conducted with electronic medical record data from the VHA, which included type of clinic encounter, ICD-9-CM diagnostic codes, prescription fills, laboratory results, vital signs and demographic measures. Data included patients with encounters at a PTSD specialty health clinic at one of five VHA medical centers across the United States between fiscal years (FY) 2008 and 2012, with follow-up continuing through FY2015. The study procedures were reviewed and approved by the Saint Louis University and Harry S. Truman Memorial Veterans' Hospital institutional review boards.

A random selection of 5,916 patients from a total of 17,476 patients 18-70 years of age, with ≥ 2 visits to PTSD specialty care in FY2008-2012, and a diagnosis of PTSD were selected. Demographic comparisons indicated that average age and distributions of gender, marital status, race, and insurance status were similar in the random and overall sample. A PTSD diagnosis was present if there were at least two outpatient visits in a 12-month period or one inpatient stay with ICD-9-CM code 309.81. This algorithm has good positive predictive value compared to a gold standard PTSD Checklist (PCL) score ≥50 (Gravely et al., 2011), and good agreement with lifetime diagnosis per the Structured Clinical Interview for DSM-IV (Holowka et al., 2014).

Patients were then required to have a PCL ≥ 50, above the threshold for probable PTSD (Monson et al., 2008; National Center for PTSD, 2012), in FY2009 -2014. This allowed for an 'exposure year' to measure PCL change after the first PCL ≥ 50, and a year prior to measure prevalent depression. Prevalent depression (ICD-9-CM: 296.2x, 296.3x, 311) was defined as a single inpatient stay or at least two outpatient codes in a 12-month period where the second outpatient code must have occurred in the year prior to PCL ≥ 50. This algorithm has excellent agreement with patient reported depression and manual chart abstraction (Frayne et al., 2010;Solberg et al., 2006). Patients were further required to have a PCL at least 8 weeks after in the 'exposure year' and depression in the year prior to the first PCL ≥

50. Finally, patients must have had at least one fill for an antidepressant medication (ADM) in the 'exposure year', leaving a final analytic sample of 742. See e-Figure 1 for sample selection.

Variable Definitions

Exposure: PCL Change—The PCL measures PTSD symptoms on a 17-item self-report measure based on DSM-IV criteria (Weathers et al., 1991). Participants rate how much they have been bothered by each symptom over the last month on a scale from 1=Not at all to 5=Extremely. Total symptom score ranges from 17 to 85. We did not distinguish whether scores were from the PCL-Military, PCL-Civilian, and PCL-Specific versions. The PCL has been shown to have good internal consistency, test-retest reliability, and convergent validity (Blanchard et al., 1996; Ruggiero et al., 2003).

PCL scores were obtained from administrative medical record data and supplemented with scores from manual chart abstraction because VHA administrative data do not capture all PCL scores in a discrete field. Abt Associates (www.abtassociates.com) conducted chart abstraction over a 6-month period on the 5,916 PTSD patients, obtaining 22,287 valid PCL scores from FY2008-2015. Administrative medical record scores were added and after removing duplicate scores, there were 4,441 patients with 26,631 PCL scores.

A meaningful reduction in PCL score was classified as a ≥20 point decrease versus a < 20 point decrease (including an increase) from the first PCL ≥ 50 to the last PCL in the 'exposure year'. This ≥20 decrease is consistent with a large, clinically meaningful PTSD improvement (Monson et al., 2008). The average number of days between first PCL ≥ 50 and the last PCL in the exposure year was 217.9 (±96.8) and median days was 213.5 (IQR=126 to 308).

Outcome: ADM adherence—ADM's included monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclics (TCAs), and non-classified ADMs (see e-table 1 for full list of drugs). ADM adherence was defined using proportion of days covered (PDC) from PCL ≥ 50 date to 12-months after (Cramer et al., 2008; Peterson et al., 2007). PDC is an adherence measure calculated as the number of days where a particular drug is available divided by the number of total days in a specified time frame. PDC ranges from 0 to 1 because unlike the medication possession ratio where the numerator is the sum of days supply for each fill in a time period, PDC does not double count covered days. Days in the exposure year when an ADM was available were identified by using fill start and end dates relative to the PCL ≥ 50 date. Overlapping days were counted as a single covered day. The PDC was the total number of ADM days covered divided by days in the exposure year. Standard thresholds were used to dichotomize PDC into adherent (≥80%) and non-adherent (< 80%) (Cramer et al., 2008; Peterson et al., 2007).

A secondary outcome indicating longest duration of continuous ADM use was created. All periods of continuous use in the exposure year were examined, where a period of continuous use stopped if there was a gap of > 30 days between fills or at the end of the exposure year.

Covariates—Detailed definitions for all variables are shown in e-table 1. Sociodemographic variables included age, race, gender, marital status and access to non-VHA health insurance. A 'missing' category was included for demographic variables to retain all cases. Age, gender, marital status, and access to non-VHA insurance were missing in 0% of cases while race was missing in 2.8% cases. Comorbid conditions were measured from one year prior to one year post PCL ≥ 50 and included anxiety disorders, sleep disorders, alcohol and drug abuse/dependence, smoking, and the Charlson-Romano comorbidity index (Romano et al., 1993). Adequate PTSD psychotherapy, defined as ≥ 9 visits in any 15-week period (Seal et al., 2010), was measured in the exposure year. Finally, an indicator of severe PTSD based on the first PCL was defined as ≥70 versus 50-69.

Propensity Score Methods—Propensity scores (PS) and inverse probability of exposure weighting (IPEW) were used to balance the distribution of potential confounders between patients with and without a clinically meaningful PCL decrease. Potential confounders are variables in Table 1, with the exception of mean first and last PCL scores which were presented for descriptive information. The PS is the probability of a PCL decrease ≥ 20 points, given covariates, that is calculated using a binary logistic regression model (Rosenbaum and Rubin, 1983). The PS is used to compute a stabilized weight (Austin and Stuart, 2015) by multiplying initial weights by the marginal probability of PCL decrease ≥20 or < 20 in the overall sample, in each respective exposure group. Stabilizing weights helps reduce bias associated with extreme weights due to increased variance and retains original sample size for analysis preserving Type I error rate. Stabilized weights should have a mean close to one and a maximum < 10, thus, weights ≥10 were trimmed (Sturmer et al., 2014). After applying IPEW, a pseudo-population is created where confounding is controlled for when variables balance between PCL decrease ≥ 20 versus < 20, indicated by a standardized mean difference (SMD%) < 10% (Austin and Stuart, 2015).

Analytic approach—All analyses were performed using SAS v9.4 (SAS institute, Cary, NC) at an alpha level of 0.05. Bivariate analyses in crude (unweighted) and weighted data assessed the relationship of PCL decrease ≥ 20 versus < 20 and potential confounders using chi-square tests for categorical variables and independent samples t-tests for continuous variables as well as SMD%. Unweighted and weighted binary logistic regression and linear regression models were used to test the association of meaningful PCL decrease with ADM adherence ≥ 80% and longest ADM duration, respectively. Robust, sandwich-type variance estimators were used to calculate confidence intervals and p-values in weighted models.

RESULTS

Overall, patients were 42.2 (±13.1) years old, 63.9% white, 43.3% married, and 18.9% had a clinically meaningful decrease in PCL score. Average first PCL was 65.1±9.2 and 34.0% had a severe initial score. Older age and high primary healthcare utilization were positively associated with PCL decrease ≥ 20 ($p<0.05$). Adequate PTSD psychotherapy was about 1.5 times more prevalent in the PCL decrease ≥ 20 versus < 20 groups (60.0% vs. 41.7%; $p<0.0001$). Average initial PCL was similar between groups but the last PCL in the exposure year was higher for PCL decrease < 20 (mean=62.7) than ≥ 20 (mean=35.2) ($p<0.0001$). No other significant differences were found. See Table 1.

Although a majority of confounders were not significantly related to PCL decrease in crude analyses, all variables with the exception of insurance, sleep disorder, and comorbidity index showed significant imbalance between groups (SMD%≥10%). IPEW balanced all confounders (SMD<10%) between groups. See e-Figure 2. Stabilized weights ranged from 0.31 to 3.87 with a mean=1.00 (±0.30) and median=0.95 (iqr=0.90-1.05). No weights were trimmed.

Descriptive outcome results and regression models are shown in Table 2. In crude analyses, 55.7% of PCL decrease ≥ 20 compared to 39.4% of PCL decrease < 20 were ADM adherent. Average longest ADM duration was 239.3 (±108.9) and 204.3 (±114.5) days in PCL decrease ≥20 versus < 20, respectively. In weighted models, there was a 78% increased likelihood of ADM adherence for PCL ≥20 versus < 20 decrease (OR=1.78; 95% CI: 1.16-2.73). Those with a clinically meaningful decrease versus not also had about 30 more days of longest continuous ADM use (B=30.22; 95% CI: 6.39, 54.04).

DISCUSSION

Patients treated in VHA PTSD specialty clinics who did vs. did not experience a clinically meaningful PCL decrease were nearly twice as likely to be adherent ADM users. These results remained largely unchanged after control for confounding. Although adherence was better in the patients with large PTSD improvement, the percent of adherent patients remained low. After controlling for confounding, only 53.5% of patients with and 39.3% without clinically meaningful PCL decrease were adherent, which is similar to the 47% of patients with comorbid depression and anxiety disorder adherent to ADMs, revealed from analysis of a private sector medical claims data (Stein et al., 2006). The percent of ADM adherent patients in those without clinically meaningful PCL reductions is similar to a previous study of patients discharged from PTSD residential treatment, of whom 34% were ADM adherent during 12-month follow-up (Lockwood et al., 2009).

Our results are limited in several ways. We do not know if patients took their medication once it was dispensed. Actual or perceived side effects of ADMs and inability to tolerate side effects are associated with early discontinuation of medication treatment (Hung, 2014). We assume poor adherence due to side-effects would be randomly distributed in patients with and without large PCL decrease and thus, unlikely to bias our analyses. We only have depression symptom scores on a small subset of patients and we are unable to draw conclusions about the effect of depression severity or magnitude of depression symptom change in those who are and are not adherent. While we controlled for a large number of confounding variables, it is possible that residual confounding exists. Last it is not known if these results generalize to non-VHA patients with PTSD.

Although we were unable to measure depression symptom change, we do estimate that about 44% of patients with clinically meaningful PCL decrease would experience depression improvement compared to 32% of patients without meaningful PCL decrease, based on prior evidence suggesting that 82.5% of ADM adherent patients have improved depression symptoms (Akerblad et al., 2006). Targeting improvements in PTSD may be an effective way to improve depression in patients with this psychiatric comorbidity (Norman et al.,

2011). Improvement in both PTSD and depression may reduce the risk of some health consequences associated with these conditions, like type 2 diabetes (Scherrer et al., 2019). Additional research is needed to determine if PTSD symptom reduction is associated with greater likelihood of adherence to non-psychotropics, such as anti-hypertensives and anti-diabetic medications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- PTSD is associated with poor antidepressant medication (ADM) adherence.
- PTSD and depressive symptoms change similarly over time.
- Significant PTSD symptom improvement is associated with greater ADM adherence.
- PTSD symptom reduction may improve depression treatment outcomes.

Table 1.

Sample characteristics overall and by PCL decrease for PTSD cases, veterans age 18-70 years with treated depression (n=742)

Variable, n(%) or mean (±sd)	Overall (n=742)	PCL dec < 20 (n=602)	PCL dec ≥ 20 (n=140)	p-value
Age (years), mean (±sd)	42.2 (±13.1)	41.6 (±13.1)	44.6 (±12.6)	.015
Male gender, n(%)	597 (80.5)	491 (81.6)	106 (75.7)	.116
Race, n(%)				
White	474 (63.9)	377 (62.6)	97 (69.3)	
Black	203 (27.4)	171 (28.4)	32 (22.9)	.174
Other	44 (5.9)	39 (6.5)	5 (3.6)	
Missing	21 (2.8)	15 (2.5)	6 (4.3)	
Married, n(%)	321 (43.3)	266 (44.2)	55 (39.3)	.292
VHA only insurance, n(%)	484 (65.2)	398 (66.1)	86 (61.4)	.294
High primary HCU, n(%)	186 (25.1)	160 (26.6)	26 (28.6)	.049
First PCL severe (≥70), n(%)	252 (34.0)	198 (32.9)	54 (38.6)	.301
First PCL, mean (±sd)	65.1 (±9.2)	64.9 (±9.2)	65.9 (±9.1)	.229
Last PCL, mean (±sd)	57.5 (±15.7)	62.7 (±11.6)	35.2 (±10.3)	<.0001
Comorbidities and treatments [a]				
Other anxiety[b], n(%)	216 (29.1)	167 (27.7)	49 (35.0)	.089
Sleep disorder, n(%)	364 (49.1)	297 (49.3)	67 (47.9)	.753
Alcohol abuse/dependence, n(%)	323 (43.5)	254 (42.2)	69 (49.3)	.127
Drug abuse/dependence, n(%)	239 (32.2)	185 (30.7)	54 (38.6)	.074
Smoking[c], n(%)	387 (52.2)	306 (50.8)	81 (57.9)	.134
Adequate PTSD psychotherapy, n(%)[d]	335 (45.2)	251 (41.7)	84 (60.0)	<.0001
Comorbidity index, n(%)				
0	461 (62.1)	378 (62.8)	83 (59.3)	
1 – 2	167 (22.5)	135 (22.4)	32 (22.9)	.627
≥ 3	114 (15.4)	89 (4.8)	25 (17.9)	

PTSD=posttraumatic stress disorder; PCL=PTSD checklist (range: 17-85); FY=fiscal year; DEC=decrease; HCU=healthcare utilization

[a]Comorbidities occur from one year prior to one year post first PCL ≥50

[b]Composite of panic disorder, obsessive compulsive disorder, social phobia, generalized anxiety disorder, anxiety not otherwise specified.

[c]Current smoker in health factors or ICD-9-CM code

[d]Measured from first PCL≥50 to one year post. Presence of ≥9 psychotherapy visits in any 15 week period.

Table 2.

Crude and weighted by inverse probability of exposure comparisons of ADM treatment adherence and PCL decrease among veterans with PTSD age 18-70 years with PTSD and treated depression. Linear and logistic regression models (n=742)

			PDC ≥ 80%[1]	Longest ADM duration (days)[2]	
	n	%	OR (95% CI)	mean (±sd)	B (95% CI)
Crude					
PCL decrease < 20	237	39.4%	reference	204.3 (±114.5)	reference
PCL decrease ≥ 20	78	55.7%	1.94 (1.34-2.81)	239.3 (±108.9)	34.97 (14.13, 55.81)
Weighted					
PCL decrease < 20	--	39.3%	reference	204.5 (±114.7)	reference
PCL decrease ≥ 20	--	53.5%	1.78 (1.16-2.73)	234.7 (±112.4)	30.22 (6.39, 54.04)

PCL=PTSD checklist; PTSD=posttraumatic stress disorder; ADM = antidepressant; OR=odds ratio; B=unstandardized regression coefficient; CI=confidence interval; PDC=proportion of days covered

[1] Logistic regression

[2] Linear regression