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Does Trauma Exposure Predict Prescription Drug Problems Beyond the Contribution of PTSD & Depression? An Analysis of the Mind Your Heart Cohort Study

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Abstract

Background—It is not clear from prior studies whether trauma exposure predicts substance use problems independent of psychiatric comorbidities. Most prior studies were cross-sectional in nature, and none focused on prescription drug problems.

Aims—To address this gap in the literature, this paper is a secondary analysis of veterans from the Mind Your Heart prospective cohort study. The primary research question is whether trauma exposure predicts prescription drug problems even after controlling for major psychiatric symptoms, such as posttraumatic stress disorder and depression.

Methods—Multinomial logistic regression was used to assess whether the 10-item lifetime Brief Trauma Questionnaire (e.g., serious car accidents, war traumas, life-threatening illness, natural disasters, physical or sexual abuse) predicts prescription drug problems as determined by a self-report categorical question (3 answer choices) over a 4-year follow-up time period (n = 661 [100%] at year 1; 83.4% at year 2; 85.9% at year 3; 78.2% at year 4).

Results—Trauma exposure was positively associated with prescription drug problems in unadjusted and age-, sex-, and race-adjusted analyses at follow-up. After accounting for PTSD (PTSD Checklist-17 Civilian Version) and depression (Patient Health Questionnaire-9) symptoms, trauma exposure was no longer associated with prescription drug problems at all time points (relative risk ratios range 0.91–1.47). These results were robust to different missing data strategies.

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Contributors: Dr. Kalapatapu completed the background literature search. Dr. Kalapatapu completed the statistical analyses with guidance from Dr. Cohen. Dr. Kalapatapu wrote the 1st draft of the paper. All authors have approved the final paper.

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Discussion—Trauma exposure was not associated with prescription drug problems over a 4-year follow-up in a prospective cohort study of veterans. Future directions include detailed measures of prescription drug problems and recruitment from community sites.

Keywords

trauma; prescription drug; veteran; depression; posttraumatic stress disorder; substance use

INTRODUCTION

Substance use problems can be the end result of a complex combination of genetic and environmental risk factors (Figure 1). Substance use problems are a tremendous public health burden in the veteran population[1–6]. Risk factors for substance use problems in veterans include trauma, depression, medical disorders, and pain, among other factors[5, 7–11]. One area of concern in veterans is prescription drug problems, which is consistent with the growing misuse of prescription drugs globally[12–15]. Prescription drug problems are associated with significant morbidity and mortality in the veteran population[16–24]. Prescription drug problems are of particular concern in veterans due to the high prevalence of mental and physical health problems[16, 25], such as chronic pain[19–21, 26, 27].

In veterans, trauma is a risk factor for many psychiatric, substance and medical problems[28–35] (Figure 1). However, not all veterans who experience trauma will go on to develop psychiatric diagnoses, such as posttraumatic stress disorder (PTSD) or depressive disorder[36–38]. The question then becomes: does exposure to trauma cause substance use problems, even after controlling for major psychiatric disorders, such as PTSD or depression? Some literature has shown that exposure to trauma without a major psychiatric disorder (such as PTSD) is not associated with substance use disorders[39–42]. But, limitations of this previous literature include the cross-sectional nature of studies and a lack of focus on prescription drug problems.

To address this gap in the literature, we conducted a secondary analysis of veterans recruited for an observational prospective cohort study. Our primary research question was: does trauma exposure predict prescription drug problems even after controlling for major psychiatric symptoms, such as PTSD and depression? A previous publication[43] evaluated this research question in a cohort of veterans and non-veterans with coronary heart disease but did not focus on prescription drug problems specifically. To maintain consistency and help with replicability in the literature, we controlled for the same covariates as the prior publication. We hypothesized that trauma exposure would predict prescription drug problems, even after controlling for PTSD and depression. We also examined several missing data strategies to account for loss to follow-up in these longitudinal analyses and evaluate the robustness of our findings.

METHODS

Overall Study Design

The original Mind Your Heart Study was designed to understand how PTSD impacts physical health, particularly cardiovascular health[44–50]. This observational prospective cohort study enrolled nearly 750 veterans between 2008 and 2010. Each participant underwent cardiac stress tests and extensive baseline mental and physical health assessments. Participants continued to be followed with yearly telephone interviews to assess PTSD symptoms and physical health, including cardiac events and hospitalizations.

Study Setting

This outpatient study recruited participants from the San Francisco Veterans Affairs Medical Center (SFVAMC) in San Francisco, California, USA, and the Veterans Affairs Palo Alto Health Care System (VAPAHCS) in Palo Alto, California, USA[49]. The institutional review boards at the University of California, San Francisco and the SFVAMC approved this study. All participants provided written informed consent.

Study Population

Participants were recruited through advertisements and mailings to patients from outpatient clinics at the SFVAMC and the VAPAHCS. Inclusion criteria were as follows: All participants needed to be over the age of 18 at the time of recruitment. Exclusion criteria were as follows: 1) inability to walk one block; 2) acute coronary event within the previous 6 months; 3) planning to move out of the area within the following 3 years; 4) lack of a stable mailing address or contact information.

Study Measurements

The full list of assessments can be found in previous publications of the Mind Your Heart Study[44–50]. For this secondary analysis, our primary independent variable was the Brief Trauma Questionnaire (BTQ). This 10-item self-report questionnaire[51, 52] (scores range from 0 to 10) screens for different types of lifetime traumatic experiences, such as serious car accidents, war traumas, life-threatening illness, natural disasters, physical or sexual abuse, and exposure to violent death. The primary dependent variable of Prescription Drug Problems was the question: “Have you ever felt you wanted to or needed to cut down on your use of prescription drugs (such as pain killers, sedatives, or tranquilizers)?” The three answer choices are: “Yes, during the last year,” “Yes, but not in the last year,” and “No.”

Self-reported demographic variables included age, sex, and race. The Clinician Administered PTSD Scale (CAPS, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition), a diagnostic structured interview administered by a clinician, was used to determine a diagnosis of PTSD[53]. PTSD symptoms were quantified with the 17-item self-report PTSD Checklist-17 Civilian Version (PCL)[54] (scores range from 17 to 85). Depressive symptoms were quantified with the 9-item self-report Patient Health Questionnaire-9 (PHQ-9)[55] (scores range from 0 to 27). Military history, medical problems and medication use were collected via self-report.

Statistical Analysis

Stata/SE version 14.2 (College Station, TX; update level 3/16/2017) was used to estimate and test all statistical models. Descriptive statistics were initially conducted on all variables. Unadjusted and adjusted analyses were then conducted. The variables selected for inclusion in the adjusted analyses were based on the previous publication on this topic[43] and depicted using a directed acyclic graph (DAG)[56] (using http://dagitty.net/). Using a DAG allows for a graphical representation of causal effects among variables[57, 58]. Traditional methods of adjusting for confounding may miss or even introduce biases such as selection bias and collider bias, which can be minimized by using more modern graphical methods of adjustment such as a DAG[59]. Age, sex and race were conceptualized as confounding variables. PTSD and depressive symptoms were conceptualized as mediating variables of trauma exposure (Figure 2).

Analyses were partially adjusted for baseline age, baseline sex and baseline race. Then, analyses were fully adjusted for baseline age, baseline sex, baseline race, year-updated PCL sum score and year-updated PHQ-9 score. Results with P_2-values < 0.05 were initially considered as statistically significant (P_2 = 2-sided P). Then, regarding multiple correction, the False Discovery Rate (FDR) method in Stata/SE version 14.2 (author Roger Newson, King's College, London, UK) was used for multiple comparison correction of any significant analyses. Specifically, the liu1, liu2, simes, yekutieli, and krieger methods with the smileplot option were tried.

Since the primary dependent variable was a 3-level categorical variable, multinomial logistic regression was used for the main analyses. To assess model fit, the "fitstat" command in Stata was used for the multinomial logistic regression analyses[60]. Among the 3 models (unadjusted, partially adjusted, fully adjusted) for each follow-up year of analysis, the Akaike's Information Criterion/sample size (AIC/N) value was used to compare AIC statistics since the sample sizes differed in each model. The fully adjusted model had the smallest Akaike's Information Criterion/sample size (AIC/N) value, which was considered the best fitting model among the 3 models. The "mlogtest" command was used to conduct either a likelihood-ratio or Wald test of the null hypothesis that the coefficients of the variable equal zero across all equations.

Two different missing data strategies[58] were used to assess the effect of loss to follow-up over the 4-year period on the fully adjusted analyses. First, since mixed-model analyses use maximum likelihood methods which preclude the need to model the missingness mechanism, the "gsem" command (generalized structural equation model) in Stata for multinomial logistic regression was used to repeat the fully adjusted analyses. Second, multiple imputation using iterative chained equations imputation (100 imputations) was used to build models to impute the missing outcomes. All missing data analyses were fully adjusted for baseline age, baseline sex, baseline race, year-updated PCL sum score and year-updated PHQ-9 score.

RESULTS

Description of Study Participants

Table 1 presents a description of the study participants. Study participants were mostly Caucasian men in their late 50's, served in the Army and the Vietnam War, and served for a mean of 5.9 years. Most study participants had back problems and arthritis/gout/joint problems. The BTQ median score was 5. The distribution of responses to the Prescription Drug Problems question varied among the 4 follow-up time points. The mean PCL sum scores at all time points indicate that participants were in the moderate severity range of PTSD symptoms. The mean PHQ-9 scores at all time points indicate that participants were in the mild severity range of depression symptoms.

Unadjusted Analyses

The interpretation of the relative risk ratio (RRR) reported for all results in Table 2 is: For each increase in BTQ score by one point, the relative risk for responding either "yes, but not in the last year" or "yes, during the last year," compared to responding "no," would be expected to increase by the point estimate reported in the table. Standard errors, 95% confidence intervals, and P_2-values are reported for all point estimates.

In unadjusted analyses, all RRRs were statistically significant at $P_2 < 0.05$ at all follow-up time points (Table 2), except for "yes, but not in the last year" for year 3 follow-up ($P_2 = 0.05$). The significant unadjusted analyses at $P_2 < 0.05$ remained significant even after trying various FDR multiple comparison correction methods (lowest corrected overall critical $P_2 = 0.0167$ with the yekutieli method).

Partially and Fully Adjusted Analyses

In analyses partially adjusted for baseline age, baseline sex and baseline race, all RRRs were statistically significant at $P_2 < 0.05$ at all follow-up time points (Table 2), except for "yes, but not in the last year" for year 4 follow-up ($P_2 = 0.06$). After trying various FDR multiple comparison correction methods, the partially adjusted analyses that remained significant (lowest corrected overall critical $P_2 = 0.0011$ with the yekutieli method) include: "yes, during the last year" for year 1 follow-up, "yes, but not in the last year" and "yes, during the last year" for year 2 follow-up, and "yes, during the last year" for year 3 follow-up. The remaining partially adjusted analyses were no longer significant.

In analyses fully adjusted for baseline age, baseline sex, baseline race, year-updated PCL sum score and year-updated PHQ-9 score, RRRs were statistically significant at $P_2 < 0.05$ at year 1 follow-up for "yes, during the last year" and at year 2 follow-up for "yes, but not in the last year." The remaining fully adjusted analyses were not statistically significant at $P_2 < 0.05$ (Table 2). After trying various FDR multiple comparison correction methods, none of the fully adjusted analyses remained significant (lowest corrected overall critical $P_2 = 0.0008$ with the yekutieli method).

The statistically significant associations between the baseline BTQ score and the year-updated PCL sum score are as follows: year 1 $\beta = 3.22$ (standard error [SE] 0.27, $P_2 <$

0.001, 95% confidence interval [CI] 2.68–3.76); year 2 β = 3.51 (SE 0.31, $P_2 < 0.001$, 95% CI 2.89–4.12); year 3 β = 3.19 (SE 0.30, $P_2 < 0.001$, 95% CI 2.60–3.77); year 4 β = 3.45 (SE 0.31, $P_2 < 0.001$, 95% CI 2.86–4.05). The Pearson's correlation coefficients between the baseline BTQ score and the year-updated PCL sum score are as follows: year 1 = 0.4628; year 2 = 0.4334; year 3 = 0.4531; year 4 = 0.4336. The statistically significant associations between the baseline BTQ score and the year-updated PHQ-9 score are as follows: year 1 β = 0.95 (SE 0.11, $P_2 < 0.001$, 95% CI 0.74–1.17); year 2 β = 1.11 (SE 0.12, $P_2 < 0.001$, 95% CI 0.88–1.33); year 3 β = 1.02 (SE 0.11, $P_2 < 0.001$, 95% CI 0.80–1.24); year 4 β = 0.99 (SE 0.11, $P_2 < 0.001$, 95% CI 0.78–1.22).

Fully Adjusted Analyses with Different Missing Data Strategies

There was loss to follow-up over the 4-year period due to mortality and lack of response for the interviews, which is reflected in the decreased sample size for the primary outcome variable ($n = 681$ at year 1 follow-up to $n = 528$ at year 4 follow-up) (Tables 1 & 2). Using mixed-model analyses and multiple imputation to assess the effect of this loss to follow-up, the results remain the same as in the fully adjusted analyses. Though some of the RRRs were statistically significant at $P_2 < 0.05$ (year 1 follow-up for "yes, during the last year" and year 2 follow-up for "yes, but not in the last year"), these analyses would no longer be significant after trying various FDR multiple comparison correction methods (lowest corrected overall critical $P_2 = 0.0008$ with the yekutieli method).

Prescription Drugs

To give a sense of the actual prescription drugs that might be problematic for participants, Table 3 lists some of the prescription drug medications that were self-reported by participants using a checklist format at baseline. Opioids, benzodiazepines, antidepressants, antipsychotics, and muscle relaxants are reported.

DISCUSSION

In this secondary analysis of a prospective cohort study of veterans, trauma exposure was positively associated with prescription drug problems in unadjusted analyses at follow-up and after adjusting for demographics. However, after also accounting for PTSD and depression symptoms (which were both independently and significantly associated with trauma exposure), trauma exposure was no longer associated with prescription drug problems at all follow-up time points. These results were robust to different missing data strategies. The RRRs from the unadjusted, partially adjusted and fully adjusted analyses would be considered to be, at best, small effect sizes.

These results differ from prior work finding trauma exposure predicted substance use independent of PTSD and depression in a cohort of patients with cardiovascular disease[43]. However, the results are consistent with some literature on this topic[39–42], though prescription drug problems have not been specifically addressed. One potential explanation for the difference in results is that in this analysis, prescription drug "problems" were analyzed rather than prescription drug "use disorders." Trauma exposure may be more

relevant to the development of a full substance use disorder, rather than subthreshold substance problems.

A second potential explanation for the lack of association in this analysis is that being diagnosed with PTSD may identify other risk factors (i.e., shared diathesis[39]) that are associated with substance use problems. As a result, when PTSD is controlled for in analyses, these other unmeasured risk factors may also be controlled for and substance use problems are no longer associated with trauma exposure. A final potential explanation is that individuals who are exposed to trauma and diagnosed with PTSD are using substances as a way to cope with the trauma[40]. Those who don't rise to the threshold of being diagnosed with PTSD may not resort to substances to cope with trauma. Thus, controlling for PTSD would lead to a lack of association between trauma exposure and substance use problems.

Clinically, these negative findings suggest that screening for a formal diagnosis for PTSD or depression is an integral next step when eliciting a history of trauma during clinical interviews. Having a major psychiatric diagnosis like PTSD or depression may suggest the presence of other risk factors that might increase the probability of substance use problems.

A separate observation regarding the decrease in endorsement of prescription drug problems over the 4-year follow-up period is that in addition to a potential healthy survivor bias, the drop-off may be due to a change in VA prescribing practices of medications. For example, the VA/Department of Defense Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain[61] gives strategies on how to limit doses of opioids long-term. The presence of such guidelines may have likely motivated VA clinical treatment providers to be more cautious in prescribing medications in recent years.

Regarding multiple comparison correction, some researchers might suggest that such correction in this type of dataset is needless since a palette of statistical models on the same research question at multiple time points is being tested. Even if the conventional $P_2 < 0.05$ cut-off for statistical significance is used, only two of the fully adjusted analyses (Table 2) would be significant. However, it is conceptually unclear how the $P_2 = 0.003$ year 1 follow-up result for "Yes, during the last year" and the $P_2 = 0.025$ year 2 follow-up result for "Yes, but not during the last year" fit into a coherent story with the other results that are well above the $P_2 < 0.05$ cut-off. The 2016 American Statistical Association's Statement on Statistical Significance and P-Values[62] discuss the complexities of using such conventional cut-offs.

Strengths

This paper has several strengths. First, the large sample size in the observational study allowed for sufficient statistical power to analyze the research question. Second, the same covariates as in a previous publication were used in this paper. This helps allow for consistency in the literature. Third, a DAG was able to explicitly categorize the variables that were controlled in the multinomial regression analyses. Such graphical representations of variables can similarly help maintain consistency by future researchers in the literature. Finally, different missing data strategies were used to assess whether the adjusted analyses were robust.

Limitations

This paper inevitably has several limitations. First, this was a post-hoc analysis, and the research question asked in this secondary analysis was not considered when the primary study was originally designed. Second, the single-item self-report question that was used in the Mind Your Heart Study may not have been detailed enough to capture all prescription drug problems.

Third, though several medications are listed in Table 3, these self-reported medications cannot be assumed to be the medications that participants wanted to or needed to cut down on use. Duration and dose of these medications were not captured. Similarly, though various medical problems are listed in Table 1, this study is not able to make a definitive causal inference connection between a particular medical problem and the use of a particular medication.

Fourth, a lack of illegal drug use was only captured via self-report and not via urine toxicology screening. Fifth, the primary dependent variable is faulty in that a participant could want to cut down on their use of prescription drugs for reasons other than those related to misuse. This item is not a pure measure of prescription drug problems. Finally, there was no baseline assessment of prescription drug problems, so it is unclear how prescription drug problems changed from baseline to year 1 follow-up.

CONCLUSIONS

Veterans with greater trauma exposure were more likely to endorse prescription drug problems over a 4-year period. However, trauma exposure was not associated with prescription drug problems after adjusting for PTSD and depression symptoms. Future directions include more detailed measures of prescription drug problems, formally screening for prescription drug use disorders and recruiting veterans from community sites.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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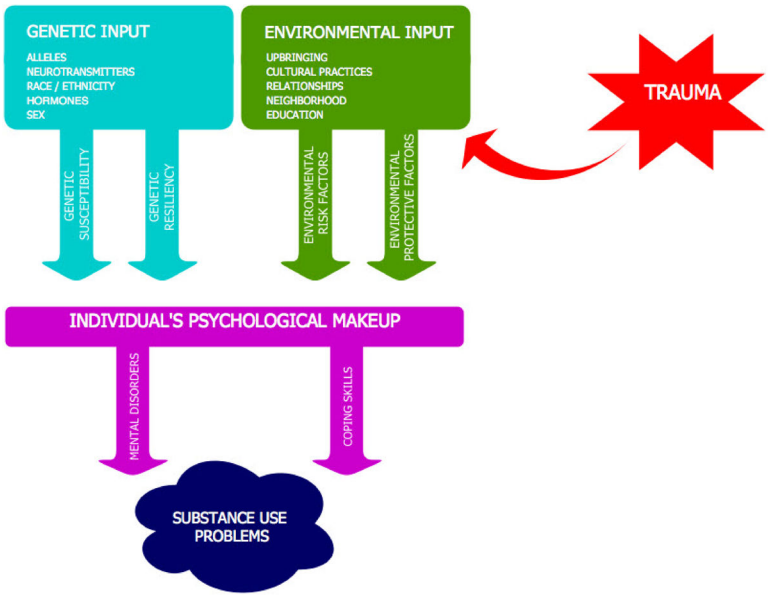

Figure 1.
Conceptual Model of Trauma and Substance Use Problems.

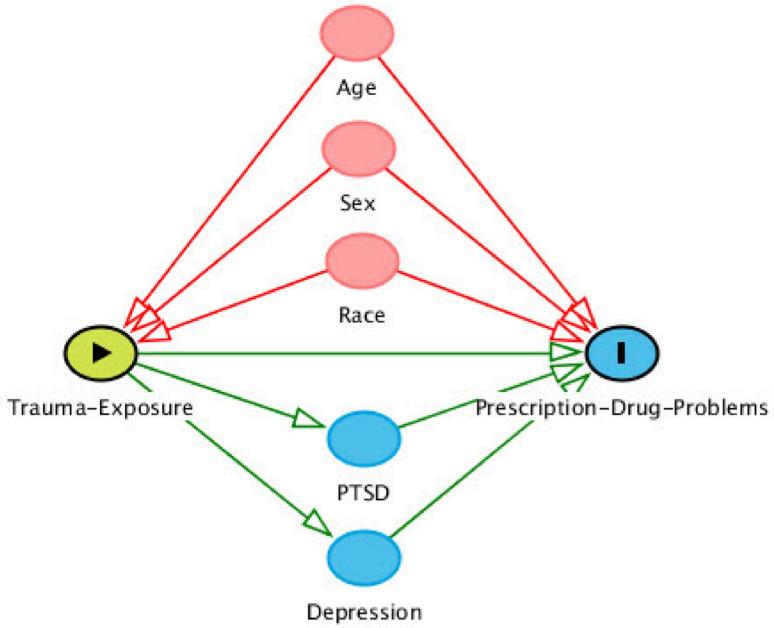

Figure 2.
Variable Selection for Regression Models based on a Directed Acyclic Graph (DAG).

Table 1

Description of Veteran Participants.

		Baseline Mean (S.D.[a]) or %	Year 1 Mean (S.D.) or %	Year 2 Mean (S.D.) or %	Year 3 Mean (S.D.) or %	Year 4 Mean (S.D.) or %
Age in years (*n* = 747)		58.4 (11.3)				
% Male (*n* = 747)		94.1%				
Ethnicity (*n* = 735)	% Caucasian	58.8%				
	% African-American	21.8%				
	% Asian	8.8%				
	% Latino	7.6%				
	% Other	3.0%				
Military History	% Gulf War (*n* = 676)	2.7%				
	% Korean War (*n* = 676)	3.0%				
	% Vietnam War (*n* = 676)	36.4%				
	% World War II (*n* = 676)	2.1%				
	% Air Force (*n* = 676)	11.1%				
	% Army (*n* = 676)	50.4%				
	% Marine (*n* = 676)	13.8%				
	% Navy (*n* = 676)	19.1%				
	Years in Service (*n* = 676)	5.9 (5.9)				
Medical Problems	% Arthritis/gout/joint problems (*n* = 739)	38.4%				
	% Back problems (*n* = 737)	50.2%				
	% Cancer diagnosis (*n* = 737)	14.4%				
	% Osteoporosis (*n* = 737)	9.5%				
	% Pancreatitis (*n* = 738)	2.7%				
	% Peripheral vascular disease (*n* = 738)	3.1%				
Posttraumatic Stress Disorder Checklist (PCL) Sum score		41.1 (18.4) *(n* = 743)	40.5 (18.7) *(n* = 681)	40.2 (19.5) *(n* = 567)	39.7 (18.7) *(n* = 583)	39.5 (18.9) *(n* = 531)
Patient Health Questionnaire-9 (PHQ-9) score		7.1 (6.0) *(n* = 742)	8.4 (7.2) *(n* = 677)	7.7 (7.0) *(n* = 567)	7.8 (6.9) *(n* = 582)	7.6 (6.6) *(n* = 532)
Brief Trauma Questionnaire (BTQ) score		Median 5, IQR[b] 3–6 Total Range 0–10 *(n* = 747)				

		Baseline Mean (S.D.[a]) or %	Year 1 Mean (S.D.) or %	Year 2 Mean (S.D.) or %	Year 3 Mean (S.D.) or %	Year 4 Mean (S.D.) or %
Prescription Drug Problems	"No"		59.5% (*n* = 405)	73.1% (*n* = 415)	72.8% (*n* = 422)	73.5% (*n* = 388)
	"Yes, but not in the last year"		4.4% (*n* = 30)	5.8% (*n* = 33)	6.4% (*n* = 37)	7.2% (*n* = 38)
	"Yes, during the last year"		36.1% (*n* = 246)	21.1% (*n* = 120)	20.9% (*n* = 121)	19.3% (*n* = 102)

[a] S.D. = Standard Deviation

[b] IQR = Interquartile Range (25% to 75%)

Table 2

Association between Baseline Brief Trauma Questionnaire score and Follow-Up Prescription Drug Problems in Veterans.

	"Yes, but not in the last year"[f] [Relative risk ratio (standard error), 95% confidence interval, P_2-value]	"Yes, during the last year"[f] [Relative risk ratio (standard error), 95% confidence interval, P_2-value]
Year 1[a] $n = 679$	1.19 (0.10), 1.02–1.40, $P_2 = 0.031$	1.22 (0.04), 1.14–1.31, $P_2 < 0.001$
Year 2[a] $n = 567$	1.35 (0.11), 1.15–1.58, $P_2 < 0.001$	1.14 (0.05), 1.05–1.25, $P_2 = 0.003$
Year 3[a] $n = 579$	1.15 (0.08), 1.00–1.33, $P_2 = 0.05$	1.22 (0.05), 1.12–1.34, $P_2 < 0.001$
Year 4[a] $n = 527$	1.17 (0.08), 1.01–1.35, $P_2 = 0.032$	1.15 (0.05), 1.05–1.26, $P_2 = 0.003$
Year 1[b] $n = 668$	1.20 (0.10), 1.03–1.41, $P_2 = 0.024$	1.24 (0.05), 1.16–1.34, $P_2 < 0.001$
Year 2[b] $n = 560$	1.33 (0.11), 1.12–1.56, $P_2 = 0.001$	1.15 (0.05), 1.05–1.26, $P_2 = 0.002$
Year 3[b] $n = 569$	1.16 (0.09), 1.00–1.34, $P_2 = 0.046$	1.22 (0.06), 1.11–1.33, $P_2 < 0.001$
Year 4[b] $n = 519$	1.15 (0.08), 0.99–1.33, $P_2 = 0.06$	1.15 (0.06), 1.05–1.27, $P_2 = 0.003$
Year 1[c] $n = 661$	1.12 (0.10), 0.94–1.33, $P_2 = 0.20$	1.13 (0.05), 1.04–1.22, $P_2 = 0.003$
Year 2[c] $n = 551$	1.23 (0.11), 1.03–1.47, $P_2 = 0.025$	1.02 (0.05), 0.92–1.13, $P_2 = 0.73$
Year 3[c] $n = 568$	1.07 (0.09), 0.91–1.25, $P_2 = 0.44$	1.07 (0.05), 0.97–1.19, $P_2 = 0.18$
Year 4[c] $n = 517$	1.08 (0.09), 0.92–1.26, $P_2 = 0.36$	1.03 (0.06), 0.92–1.14, $P_2 = 0.63$
Year 1[d] $n = 661$	1.12 (0.10), 0.94–1.33, $P_2 = 0.20$	1.13 (0.05), 1.04–1.22, $P_2 = 0.003$
Year 2[d] $n = 551$	1.23 (0.11), 1.03–1.47, $P_2 = 0.025$	1.02 (0.05), 0.92–1.13, $P_2 = 0.73$
Year 3[d] $n = 568$	1.07 (0.09), 0.91–1.25, $P_2 = 0.44$	1.07 (0.05), 0.97–1.19, $P_2 = 0.18$
Year 4[d] $n = 517$	1.08 (0.09), 0.92–1.26, $P_2 = 0.36$	1.03 (0.06), 0.92–1.14, $P_2 = 0.63$
Year 1[e] $n = 734$	1.10 (0.09), 0.93–1.31, $P_2 = 0.26$	1.13 (0.04), 1.04–1.22, $P_2 = 0.003$
Year 2[e] $n = 734$	1.21 (0.11), 1.01–1.45, $P_2 = 0.04$	1.01 (0.05), 0.91–1.12, $P_2 = 0.81$
Year 3[e] $n = 734$	1.09 (0.09), 0.93–1.27, $P_2 = 0.30$	1.07 (0.05), 0.97–1.18, $P_2 = 0.18$
Year 4[e] $n = 734$	1.07 (0.09), 0.91–1.26, $P_2 = 0.39$	1.03 (0.05), 0.93–1.14, $P_2 = 0.56$

[a] Unadjusted analyses

[b] Adjusted for baseline age, baseline sex, baseline race

[c] Adjusted for baseline age, baseline sex, baseline race, year-updated PCL sum score, year-updated PHQ-9 score

[d] Maximum Likelihood – Mixed Model Analyses (Generalized Structural Equation)

[e] Multiple Imputation – Iterative Chained Equations Imputation Analyses

[f] Reference group is an answer of "no"

Table 3

Prescription Drugs Self-Reported by Veteran Participants via Checklist at Baseline.

	Medication Name	% from *n* = 744
Opioids	Acetaminophen/Codeine	1.75%
	Acetaminophen/Hydrocodone	8.60%
	Acetaminophen/Oxycodone	2.15%
	Morphine	2.28%
	Oxycodone	3.76%
Benzodiazepines	Diazepam	0.94%
	Lorazepam	2.15%
Antidepressants	Amitriptyline	1.75%
	Bupropion	7.93%
	Citalopram	7.53%
	Fluoxetine	2.02%
	Mirtazapine	4.17%
	Paroxetine	2.15%
	Sertraline	4.57%
	Trazodone	11.02%
Antipsychotics	Quetiapine	3.49%
Muscle Relaxants	Cyclobenzaprine	2.82%