Observational Evidence for Buprenorphine's Impact on Posttraumatic Stress Symptoms in Veterans With Chronic Pain and Opioid Use Disorder

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ABSTRACT

Objective: Posttraumatic stress disorder (PTSD), chronic pain, and substance use disorders are prevalent co-occurring conditions that are challenging to treat individually, and there is no evidence-based treatment for all 3. Buprenorphine, used to treat opioid use disorder and chronic pain, is a partial nociceptin opioid receptor agonist. In preclinical studies, a nociceptin opioid receptor agonist was shown to mitigate PTSD symptoms in acute trauma. We compared buprenorphine to other opioid medications in its impact on PTSD symptoms in patients with chronic pain and opioid and/or other substance use disorders.

Method: We assembled a retrospective cohort of 382 Iraq and Afghanistan veterans in US Department of Veterans Affairs health care from October 1, 2007, to July 29, 2013, with *ICD-9-CM* diagnoses of PTSD, chronic pain, and substance use disorders. We used time-varying general estimating equation models to assess the primary outcome, which was change in PTSD symptoms (measured using the PTSD Checklist and the Primary Care PTSD Screen) among veterans initiated on sublingual buprenorphine versus those maintained on moderately high-dose opioid therapy.

Results: Twice as many veterans in the buprenorphine group (23.7%) compared to those in the opioid therapy group (11.7%) experienced improvement in PTSD symptoms ($P = .001$). Compared to veterans in the opioid therapy group, veterans receiving buprenorphine showed significant improvement in PTSD symptoms after 8 months, with increasing improvement up to 24 months (incidence rate ratio = 1.79; 95% CI, 1.16–2.77; $P = .009$). There were no differences in the longitudinal course of pain ratings between groups.

Conclusions: This observational study is the first to report an incidental effect of buprenorphine compared to opioid therapy in improving PTSD symptoms in veterans.

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The triad of posttraumatic stress disorder (PTSD), chronic pain, and substance use disorders is prevalent, particularly among war veterans.[1,2] Indeed, among half a million US veterans who served in Iraq and Afghanistan and received diagnoses of chronic pain, those with PTSD were significantly more likely to receive prescription opioids for chronic pain, exhibit prescription opioid misuse, and be at heightened risk for serious adverse clinical outcomes including overdose, injuries, and suicide.[2] These considerably worse outcomes may, in part, be explained by the observation that Iraq and Afghanistan veterans with comorbid chronic pain and PTSD experience higher pain severity and pain catastrophizing than those with chronic pain alone.[3]

The use and overuse of substances, including opioids, are not limited to the veteran population as there have been similar reports in community-based populations. In a community-based sample of patients with chronic pain, those with PTSD diagnoses were significantly more likely than those without PTSD to have been prescribed opioids (vs nonopioid analgesics).[4] The co-occurrence of PTSD and chronic pain complicated by substance use disorders may be driven, in part, by the need to self-medicate PTSD symptoms. For instance, patients with PTSD report a reduction in the intrusive and hyperarousal symptoms of PTSD after using opioids.[5,6] In addition, this clinical triad may also be explained by shared underlying psychopathology and neurobiology,[1,7–10] as well as by PTSD-related disruption of the endogenous opioid system.[11,12]

Individually, treatment of PTSD, chronic pain, and substance use disorders remains challenging, and, to date, there is no single evidence-based treatment for all 3 conditions. Observational studies in adult and pediatric patient populations who have experienced *acute* trauma and physical pain (eg, pediatric burn victims, wounded soldiers) have shown that those who received morphine (opioid analgesia) for acute pain compared to those who did not were less likely to develop symptoms of PTSD.[13–15] Nevertheless, the long-term use of morphine and other full μ-opioid receptor agonists to treat *chronic* PTSD symptoms is limited by their potential for abuse and addiction. Of note, in a recent study of a mouse model of acute trauma, a selective nociceptin opioid receptor agonist blocked fear memory conditioning in the amygdala and prevented or attenuated symptoms of PTSD without the undesirable reward effects of opioids because the drug did not bind to the μ-opioid receptor.[16]

A similar US Food and Drug Administration (FDA)–approved partial nociceptin opioid receptor agonist for humans, buprenorphine, has demonstrated efficacy for the treatment of opioid use disorder and chronic pain.[17–19] Also, as a partial μ-opioid receptor agonist, buprenorphine has fewer of the undesirable reward effects of full μ-opioid receptor agonists, such as morphine or methadone, and therefore is less likely to result in addiction.[19] Buprenorphine also antagonizes the

κ-opioid receptor that produces dysphoria when activated, which may explain its observed antidepressant effect[20,21] even in older adults with treatment-resistant depression.[22] Thus, patients who suffer from chronic PTSD (which is highly comorbid with depression[23]), chronic pain, and opioid use disorder may benefit from buprenorphine therapy relative to other available opioid analgesics.[22] To our knowledge, however, there is only 1 case report[24] in which buprenorphine, used for opioid replacement therapy, incidentally improved chronic PTSD symptoms. Buprenorphine's efficacy in the treatment of opioid use disorder and chronic pain is well established,[17–19] but no study to date has examined buprenorphine's effect on chronic PTSD symptoms.

We conducted a preliminary observational study of several hundred Iraq and Afghanistan veterans in the US Department of Veterans Affairs (VA) health care system diagnosed with chronic comorbid PTSD, pain, and substance use disorders, including opioid use disorder. We explored whether sublingual buprenorphine incidentally improved PTSD symptoms in veterans compared to a similar group of veterans maintained on a moderately high-dose opioid therapy. Our hypothesis was that among veterans with PTSD and chronic pain diagnoses, those initiating buprenorphine would have reductions in PTSD symptoms compared to veterans maintained on opioid therapy.

Clinical Points

- Posttraumatic stress disorder (PTSD), chronic pain, and substance use disorders are prevalent co-occurring conditions that are challenging to treat individually, and there is no evidence-based treatment for all 3.
- Buprenorphine is a Food and Drug Administration–approved medication for the treatment of opioid use disorder and chronic pain (transdermal formulation), but its impact on PTSD symptoms in the relatively large number of patients with all 3 co-occurring conditions has not been studied, which could be useful information for clinicians caring for these complex patients.
- In a retrospective cohort of veterans with PTSD, chronic pain, and substance use disorders, observational evidence supported an incidental improvement in PTSD symptoms with buprenorphine compared to opioid therapy. This finding could provide useful information for clinicians caring for these complex patients.

METHOD

Data Source and Population

Department of Veterans Affairs administrative databases were used to conduct retrospective data analyses. Access to VA data was requested and approved via the VA Data Access Request Tracker (DART). We linked a national database of Iraq and Afghanistan veterans who have separated from US military service and enrolled in VA health care to (1) the Corporate Data Warehouse, which contains pharmacy and patient health screen data and (2) the VA National Patient Care Database, which provides VA clinic visit dates and associated diagnostic codes from the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*). We chose October 1, 2007, as a study start date because during this year the VA started systematically conducting population-based mental health screening of Iraq and Afghanistan veterans.[25] The study end date was July 29, 2013.

We restricted our analysis to veterans who had at least 2 prior diagnoses of PTSD (*ICD-9-CM* code 309.81) on 2 separate clinical visits. Second, we also required a positive PTSD screen at baseline indicating current PTSD symptoms and at least 2 follow-up PTSD screens after buprenorphine initiation or continuation of opioid therapy, respectively. We defined chronic pain as having received the same noncancer pain diagnostic code on 2 or more occasions for a minimum of 90 days.[2] Finally, we included veterans who had received diagnoses of substance use disorders within the context of at least 2 separate clinical encounters at a VA health care facility. Diagnoses of substance use disorders included alcohol and/or substance abuse or dependence diagnoses, including opioid use disorder. We included this broad substance use disorders diagnostic category because prior studies have shown that substance use subcategories are not consistently specified in VA administrative data.[26] Furthermore, veterans who are prescribed opioid therapy to treat chronic pain are less likely to be coded as having a concurrent opioid use disorder.[2,26] The study was approved by the Committee on Human Research, University of California, San Francisco, and the San Francisco VA Medical Center.

Independent Study Variables

Within the retrospective cohort, we compared 2 groups of veterans: those who were initiated on buprenorphine therapy versus those who remained on opioid therapy. Specifically, the buprenorphine treatment group consisted of Iraq and Afghanistan veterans in VA health care with chronic pain, PTSD, and opioid use disorder diagnoses who initiated sublingual buprenorphine. Nearly all veterans in the buprenorphine treatment group had an opioid use disorder diagnoses (98.9%), and opioid use disorder is the only approved indication for initiating sublingual buprenorphine within the VA. Veterans in the treatment group received either of the 2 available formulations of sublingual buprenorphine (with or without naloxone). The control group consisted of Iraq and Afghanistan veterans in VA health care diagnosed with the triad of PTSD, chronic pain, and substance use disorders, including opioid use disorder. As just described, veterans with diagnoses of substance use disorders without a specific opioid use disorder code may still have an opioid use disorder, but may not be coded as such while receiving prescription opioids.[2,26] Veterans in the control group were maintained on a moderately high dose of opioid therapy (≥ 50 morphine equivalents/d) for chronic pain.[27,28]

Additional independent variables included sociodemographic and military service characteristics and

other current mental health diagnoses received within 1 year of the baseline PTSD score. Other independent covariates included self-reported pain scores (scale from 0 to 10, 10 being most severe pain), mental health treatment utilization (but not type of mental health treatment received due to limitations of administrative data), and antidepressant use. We specifically adjusted for mental health services utilization (ie, number of mental health visits) and medications (ie, antidepressants) used to treat PTSD to control for the possibility that veterans in the buprenorphine group might be more likely to receive PTSD treatment than those in the control group.

Dependent Outcome Variables: Change in PTSD Symptom Severity Scores

For the buprenorphine group, we used as the baseline measurement change in PTSD symptom severity scores first measured within 1 year prior to initiating buprenorphine and again after at least 60 days of buprenorphine treatment for opioid use disorder (to allow patients time to stabilize after buprenorphine induction). For the control group, we used as the baseline measurement the first positive PTSD score documented in the medical record after receiving opioid therapy for the first time (in VA) for at least 30 days, and during follow-up, we included all subsequent PTSD scores. All veterans included in this study were required to have had at least 90 days of follow-up time.

PTSD symptoms were assessed using the VA Primary Care PTSD Screen (PC-PTSD),[25,29] the PTSD Checklist (PCL),[30,31] or both.[32] Both measures were included in order to capture the most representative sample, given that the PC-PTSD screen is used mainly in VA primary care, whereas the PCL is used more in VA mental health settings. The PC-PTSD is a brief 4-item screen for PTSD symptoms administered annually to all veterans.[25] The screen yields binary responses (yes or no) for each of 4 PTSD symptom clusters: reexperiencing, avoidance, emotional numbing, and hyperarousal.[25,33] The PCL is a 17-item measure with each item rating the presence of a different PTSD symptom over the past month on a 5-point Likert scale, from not at all to extremely.[31] Symptoms rated as moderately or above on the PCL were considered positive. Positive PTSD symptoms clustered as 1 of the 4 PTSD symptom clusters just described. The PCL has been shown to have very good internal consistency and correlates strongly with other measures of PTSD symptoms, particularly the PC-PTSD screen as well as the gold standard Clinician-Administered PTSD Scale (CAPS).[25,30]

Symptoms from each of the 4 PTSD symptom clusters on the PCL were used to create indicators that paralleled each of the 4 symptom clusters on the PC-PTSD Screen.[32,34] Specifically, having PTSD symptoms was defined as endorsing ≥ 2 of 4 PTSD symptoms on the PC-PTSD[25] or an equivalent score (2 of 4 clusters endorsed as moderately or above) when response items were mapped from the 17-item PCL to the 4-item PC-PTSD Screen. (See Supplementary eTable 1 for details about validity of the mapping algorithm based on prior published work.[32])

Data Analyses

Separate time-varying general estimating equation models compared the buprenorphine group to the opioid therapy control group with regard to change in PTSD symptom and pain scores, using Poisson and Gaussian distributions, respectively. Poisson distribution was chosen for PTSD symptoms because our outcome measure was a count of 4 symptoms. Pain scores were modeled using a normal (Gaussian) distribution because they approximated a continuous distribution. Models were population-averaged and used auto-regressive correlation. To evaluate different rates of change between treatment groups over time, interaction terms (group × time variables) were included. After adjusting for baseline pain and PTSD scores, models were adjusted for gender, alcohol use disorder, antidepressant use, and other independent variables that differed significantly between groups in initial bivariate analyses at $P < .05$: age, race/ethnicity, marital status, and mental health services utilization during follow-up. While the prevalence of opioid use disorder was greater in the buprenorphine compared to the control group, we did not adjust for opioid use disorder because it is required and a fixed indication for the use of buprenorphine and thus highly collinear with our main independent variable. Data were prepared using SAS version 9.3 (SAS Institute, Cary, NC) and analyzed using Stata version 13.1 (StataCorp LP, College Station, Texas).

RESULTS

Of 382 Iraq and Afghanistan veterans in the sample, the mean ± SD age was 31.5 ± 7.2 years, and 2.4% were women. Compared to 205 veterans maintained on opioid therapy, the 177 who were started on buprenorphine were significantly younger, more likely to be white, never married, were likely to have attended more mental health visits during follow-up, had lower baseline pain scores, and were more likely to have received an opioid use disorder diagnosis, the primary indication for buprenorphine. There was no difference between groups with regard to baseline PTSD symptom severity, number of comorbid mental health diagnoses, or use of antidepressant medications (Table 1).

Roughly twice as many veterans in the buprenorphine group (23.7%) compared to the opioid therapy group (11.7%) showed improvement in PTSD symptoms from baseline to the initial follow-up measurement, which was a statistically significant difference between groups ($P = .001$).

In a model that was fully adjusted for age, sex, race/ethnicity, marital status, baseline PTSD and pain scores, alcohol use disorder, number of mental health visits, and antidepressant use, veterans who initiated buprenorphine showed significant improvement in PTSD symptoms beginning at 8 months, with increasing improvement up to 24 months (end of ascertainment period) compared to those in the opioid therapy group (incidence rate ratio comparing buprenorphine to opioid therapy at 24 months = 1.79;

Table 1. Baseline Characteristics of 382 Iraq and Afghanistan Veterans With PTSD, Chronic Pain, and Substance and/or Opioid Use Disorders in VA Health Care (10/1/07–7/29/13)[a]

Characteristic	Total (N = 382)		Opioids (n = 205)		Buprenorphine (n = 177)		*P* Value
Sex							
Female	9	(2.4)	6	(2.9)	3	(1.7)	
Male	373	(97.6)	199	(97.1)	174	(98.3)	.429
Age at first PTSD score, mean (SD)	31.5	(7.2)	33.7	(7.9)	29.0	(5.1)	<.001
Race and/or Ethnicity							
Nonwhite	112	(29.3)	69	(33.7)	43	(24.3)	
White	270	(70.7)	136	(66.3)	134	(75.7)	.045
Marital status							
Married	166	(43.5)	103	(50.2)	63	(35.6)	
Never married	204	(53.4)	93	(45.4)	111	(62.7)	
Divorced, widowed, or other	12	(3.1)	9	(4.4)	3	(1.7)	.002
Rank and education[b]							
Enlisted, less than baccalaureate	369	(97.4)	196	(96.6)	173	(98.3)	
Enlisted, baccalaureate or greater	6	(1.6)	4	(2.0)	2	(1.1)	
Officer, baccalaureate or greater	4	(1.1)	3	(1.5)	1	(0.6)	.554
Active duty or Reserve/National Guard							
Active duty	239	(62.6)	125	(61.0)	114	(64.4)	
Reserve/Guard	143	(37.4)	80	(39.0)	63	(35.6)	.490
Military branch							
Army	295	(77.2)	158	(77.1)	137	(77.4)	
Air Force	20	(5.2)	13	(6.3)	7	(4.0)	
Marines	51	(13.4)	25	(12.2)	26	(14.7)	
Navy	16	(4.2)	9	(4.4)	7	(4.0)	.678
Multiple deployments							
Single deployment	248	(64.9)	129	(62.9)	119	(67.2)	
Multiple deployments	134	(35.1)	76	(37.1)	58	(32.8)	.379
Total mental health visit days during follow-up, mean (SD)	38.7	(44.3)	23.5	(23.4)	56.4		
Antidepressant medications (30 days or greater)							
No	49	(12.8)	27	(13.2)	22	(12.4)	
Yes	333	(87.2)	178	(86.8)	155	(87.6)	.829
PTSD score (baseline), mean (SD)	3.7	(0.6)	3.8	(0.6)	3.7		
Pain score (baseline), mean (SD)	5.0	(3.0)	5.5	(2.8)	4.4	(3.1)	<.001
Number of comorbid mental health diagnoses (in addition to PTSD and SUD)							
0	3	(0.8)	1	(0.5)	2	(1.1)	
1	34	(8.9)	21	(10.2)	13	(7.3)	
2+	345	(90.3)	183	(89.3)	162	(91.5)	.484
Alcohol dependence or abuse							
No	94	(24.6)	46	(22.4)	48	(27.1)	
Yes	288	(75.4)	159	(77.6)	129	(72.9)	.290
Illicit drug dependence or abuse							
No	48	(12.6)	48	(23.4)	0	(0.0)	
Yes	334	(87.4)	157	(76.6)	177	(100.0)	<.001
Opioid dependence or abuse diagnosis							
No	111	(29.1)	109	(53.2)	2	(1.1)	
Yes	271	(70.9)	96	(46.8)	175	(98.9)	<.001

[a]Data are n (%) unless otherwise stated.
[b]Data are missing for 3 veterans.
Abbreviations: PTSD = posttraumatic stress disorder, SUD = substance use disorders.

95% confidence interval, 1.16–2.77; $P = .009$) (Table 2 and Figure 1). In comparison, the opioid therapy group showed a nonsignificant worsening of PTSD symptoms relative to baseline during the follow-up period (Table 2 and Figure 1). Also, there were no differences in the longitudinal course of pain ratings between groups over time (Figure 2).

Buprenorphine treatment was associated with a modest improvement of PTSD symptoms relative to baseline (on a scale from 0 to 4 on the PC-PTSD scale) over 24 months of follow-up, which was statistically significant ($P = .048$). Furthermore, there were significant within-group improvements in PTSD symptoms between the baseline measurement and 12- and 24-month follow-up (both *P* values < .05) (Table 2).

DISCUSSION

This study is the first to observe that buprenorphine therapy incidentally improved PTSD symptom severity after 8 months in a retrospective cohort of veterans with PTSD, chronic pain, and substance use disorders in comparison to a similar group of veterans maintained on conventional opioid therapy. This positive effect on PTSD symptoms, although modest, increased with increasing time on buprenorphine without an increase in pain. In contrast, there was a nonsignificant trend toward worsening of PTSD symptoms with more time on opioid therapy.

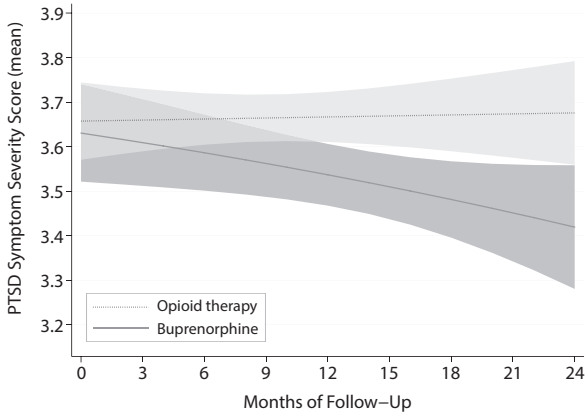
In the VA health care system, buprenorphine is prescribed primarily through specialty substance use disorder clinics (ie,

Table 2. Adjusted GEE Results Show Improvement in PTSD Symptoms in Iraq and Afghanistan Veterans With PTSD, Chronic Pain, and Substance and/or Opioid Use Disorders Initiating Buprenorphine vs Continuing Opioid Therapy[a]

	Base Model[b]		Demographics[c]		Mental Health and Utilization[d]	
Unique patients, N	382		382		382	
Total observations	1,392		1,392		1,392	
	IRR (95% CI)	*P* Value	IRR (95% CI)	*P* Value	IRR (95% CI)	*P* Value
Treatment vs control						
6 mo	1.26 (0.98–1.63)	.074	1.22 (0.94–1.59)	.136	1.23 (0.93–1.62)	.150
12 mo	1.45 (1.18–1.80)	.001	1.40 (1.12–1.74)	.003	1.39 (1.10–1.76)	.007
18 mo	1.68 (1.26–2.23)	<.001	1.59 (1.19–2.14)	.002	1.58 (1.16–2.15)	.004
24 mo	1.93 (1.27–2.94)	.002	1.82 (1.19–2.79)	.006	1.79 (1.16–2.77)	.009
Control group change from baseline						
12 mo	0.97 (0.75–1.25)	.801	0.99 (0.76–1.28)	.932	0.97 (0.75–1.26)	.836
24 mo	0.94 (0.56–1.57)	.801	0.98 (0.58–1.64)	.932	0.95 (0.56–1.60)	.836
Treatment group change from baseline						
12 mo	1.28 (1.03–1.60)	.025	1.29 (1.03–1.61)	.024	1.25 (1.00–1.57)	.048
24 mo	1.65 (1.06–2.56)	.025	1.66 (1.07–2.59)	.024	1.57 (1.00–2.45)	.048

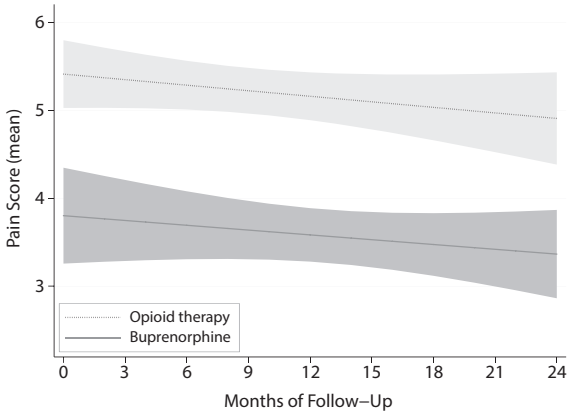
[a]GEE model results reported for regular 6- or 12-month follow-up time intervals.
[b]Base generalized estimating equation (GEE) model is adjusted only for baseline PTSD score.
[c]Adding adjustment for demographic covariates—age, sex, race/ethnicity, marital status.
[d]Adding adjustments for baseline pain rating, mental health visits during follow-up, and antidepressant use.
Abbreviations: CI = confidence interval, GEE = generalized estimating equation, IRR = incidence rate ratio, PTSD = posttraumatic stress disorder.

Figure 1. PTSD Symptom Severity Scores Among Iraq and Afghanistan Veterans[a,b]



[a]Veterans had *ICD-9-CM* diagnoses of PTSD, chronic pain, and substance use disorders, including opioid use. The opioid therapy group showed a nonsignificant worsening of PTSD symptoms relative to baseline during the follow-up period. Those who initiated buprenorphine showed a significant decrease in PTSD Symptom Severity scores over time (fully adjusted GEE model) compared with those who continued on a moderately high dose of opioid therapy. Between-group differences became statistically significant ($P < .05$) at 8 months of follow-up. Note that this is not readily apparent from the graph due to the confidence intervals representing uncertainty for the within-group changes.
[b]Lines indicate GEE model predictive margins, and the shaded regions indicate 95% confidence intervals for the model estimates.
Abbreviations: GEE = generalized estimating equation, PTSD = posttraumatic stress disorder.

Figure 2. Self-Reported Pain Scores Among Iraq and Afghanistan Veterans With PTSD[a]



[a]Veterans had *ICD-9-CM* diagnoses of PTSD, chronic pain, and substance use disorders, including opioid use. Patients who initiated buprenorphine therapy and received pain diagnoses had pain managed effectively during follow-up. Had these patients not received adequate pain treatment—relative to patients receiving chronic opioid therapy—then the lines for the 2 treatment groups would be expected to converge over time. In contrast, the 2 treatment groups had trajectories that were essentially parallel, with slopes that were not significantly different ($P = .765$), which indicates that both groups received comparable pain treatment.
[b]Lines indicate GEE model predictive margins, and the shaded regions indicate 95% confidence intervals for the model estimates.
Abbreviations: GEE = generalized estimating equation, PTSD = posttraumatic stress disorder.

opioid replacement clinics), coded as mental health clinic visits, and, to a lesser degree, is prescribed through primary care. In contrast, opioid therapy is most often prescribed through primary care. Thus, it is not surprising that the buprenorphine group had nearly twice the number of mental health visits during follow-up than the opioid therapy group, which could potentially explain this group's improvement in PTSD symptoms. Patients in the VA system typically do not receive evidence-based PTSD treatment in opioid replacement clinics, however, and we adjusted for outpatient mental health services utilization and antidepressant use in our analyses. Thus, it is unlikely that mental health

treatment explained PTSD symptom improvement in the buprenorphine group. In addition, baseline PTSD symptoms and burden of mental health comorbidity were similar in the 2 groups, although the buprenorphine group had a significantly greater proportion of patients with both drug and alcohol use disorders than the opioid therapy group. We not only adjusted for all baseline differences between the groups but also these comorbidity patterns are unlikely to explain our finding of improved PTSD symptoms in the buprenorphine group because complex polysubstance use might have predicted just the opposite, namely a worsening of PTSD symptoms over time.[26,35,36]

Finally, the opioid therapy group reported greater pain severity at baseline and continued to report higher levels of pain throughout follow-up. Chronic pain itself may trigger PTSD symptoms and could explain the finding of a slight worsening of PTSD symptoms in the opioid therapy group.[8] While we controlled for differences in baseline pain scores, future prospective trials are needed that stratify subjects with regard to pain and better delineate the longitudinal relationship between chronic pain and PTSD in those undergoing differential treatments.

Our results should be interpreted with additional caveats and should be considered preliminary and hypothesis-generating. Most importantly, we took advantage of retrospective administrative data to examine "incidental" PTSD symptom improvement in veterans initiated on buprenorphine therapy for another indication (opioid use disorder or chronic pain). This was not a dedicated controlled trial of buprenorphine treatment to examine PTSD symptom improvement, which may, in part, explain the significant, yet modest effect we observed. Second, we triangulated scores from the PCL and PC-PTSD screens to define our common primary outcome (score of 0 to 4 on the PC-PTSD screen). We took these steps, similar to another recently published study,[32] to maximize sample size, increase sensitivity to PTSD symptom change, and make our findings more generalizable to primary care settings in which buprenorphine and opioid therapy are often prescribed. Third, using retrospective data, we attempted to make the 2 groups as similar as possible—all were Iraq and Afghanistan veterans in VA health care and had PTSD diagnoses and symptoms (using valid, standard screens), chronic pain, and opioid and/or other diagnoses of substance use disorders. Nevertheless, there were likely differences that we were not able to completely adjust for in our analyses.

Further, the VA cares for relatively few women, and for this reason and because of other differences in veteran populations, caution should be used when generalizing these results to nonveteran/non-VA populations. Finally, while we were able to assess buprenorphine's association with changes in PTSD symptoms, because we used an administrative database limited to diagnostic codes and symptom scores, we were not able to assess buprenorphine's efficacy in treating more subjective outcomes such as opioid craving, addictive behavior, and physical dependence symptoms. Buprenorphine's efficacy in these domains has already been established in other studies.[19] Finally, without more sensitive measures and biomarkers, we cannot be sure that improvements in PTSD symptoms in the buprenorphine group were not mediated by stabilization of drug addiction and/or chronic pain, rather than through a specific action of buprenorphine for PTSD. Most likely, buprenorphine works in more than one way.[37] By acting on several different opioid receptors, buprenorphine may stabilize multiple neural circuits that mitigate pain and opioid craving (μ-opioid receptor), interrupt fear memory consolidation (nociceptin opioid receptor), and improve anxiety and depression symptoms (κ-opioid receptor).[16,19,20]

Considering these limitations, the results of this study remain intriguing and potentially clinically important, especially for this particularly high-risk population of patients with the triad of PTSD, chronic pain, and opioid and other substance use disorders. Unfortunately, this diagnostic triad is common among veterans as well as vulnerable nonveteran populations.[2,10,38] At this time, there are no single evidence-based treatment options for patients with all 3 conditions.[39] Moreover, these patients are extremely challenging to manage clinically and are often disabled or dysfunctional socially.[40]

Paradoxically, studies have shown that these higher-risk patients are even more likely than other lower-risk groups to receive full μ-opioid agonists (eg, oxycodone) for the treatment of chronic pain, despite clear evidence that chronic opioid therapy may exacerbate PTSD symptoms and fuel addictive behavior.[40–42] Moreover, because conventional opioids create tolerance and physical dependence, opioid doses tend to escalate over time, which can lead to hyperalgesia that in turn worsens the chronic pain condition they were originally intended to treat.[43] In more extreme cases, the continued escalation of opioids coupled with PTSD and substance use disorders can lead to accidental or intentional overdose.[2,28,44]

In contrast, unlike full μ-opioid agonists, buprenorphine, as a partial μ receptor agonist, has less reward and addiction potential and has a ceiling effect, which makes it safer and less likely to produce the same level of tolerance, physical dependence, and withdrawal symptoms of other full agonist opioids.[19,45] Buprenorphine is already FDA-approved for the treatment of opioid use disorder and chronic pain (transdermal formulation), and this study points to improvement of PTSD symptoms in patients with all 3 problems. Based on our preliminary findings, a dedicated controlled prospective trial of buprenorphine in individuals with the triple threat of chronic pain, substance use disorders (including opioid use disorder), and PTSD may help to shed more light on buprenorphine's efficacy in reducing chronic PTSD symptoms.

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Drug names: buprenorphine (Subutex, Suboxone, and others), methadone (Methadose and others), morphine (Kadian, Avinza, and others), oxycodone (Roxicodone, Oxecta, and others).

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Supplementary Material

Article Title: Observational Evidence for Buprenorphine's Impact on Posttraumatic Stress Symptoms in Veterans With Chronic Pain and Opioid Use Disorder

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List of Supplementary Material for the article

1. **eTable 1** Validity of Mapping of PCL to the PC-PTSD

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 eTable 1. Validity of mapping of PCL to the PC-PTSD

PC-PTSD Question (yes/no)	**Corresponding PCL Questions (either response rated moderately or above)**	**Percent Agreement (n=57,889 screens given on same date)**
1. Have had nightmares about it or thought about it when you did not want to?	1. Repeated, disturbing memories, thoughts, or images of a stressful experience from the past?	81.2
	2. Repeated, disturbing dreams of a stressful experience from the past?	
2. Tried hard not to think about it or went out of your way to avoid situations that reminded you of it?	6. Avoid thinking about or talking about a stressful experience from the past or avoid having feelings related to it?	81.5
	7. Avoid activities or situations because they remind you of a stressful experience from the past?	
3. Were constantly on guard, watchful, or easily startled?	16. Being "super alert" or watchful on guard?	85.8
	17. Feeling jumpy or easily startled?	
4. Felt numb or detached from others, activities, or your surroundings?	10. Feeling distant or cut off from other people?	82.0
	11. Feeling emotionally numb or being unable to have loving feelings for those close to you?	
Overall screen result (>2 symptoms endorsed)	Overall screen result (>2 symptoms endorsed)	82.5