Association of Mental Health Disorders With Prescription Opioids and High-Risk Opioid Use in US Veterans of Iraq and Afghanistan

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Greater combat exposure coupled with improvements in battlefield medicine and protective gear have resulted in large numbers of veterans of Iraq and Afghanistan surviving injuries that would have been fatal in prior wars.1-3 Veterans are returning home with comorbid mental and physical health problems.1,4 Posttraumatic stress disorder (PTSD) is the most prevalent mental health disorder among veterans of Operation Enduring Freedom (OEF, principally Afghanistan) and Operation Iraqi Freedom (OIF) who use Veterans Affairs (VA) health care,5 the largest provider of health care for these veterans. Somatic complaints, especially pain, have been strongly associated with mental health disorders, particularly PTSD, in prior-era veterans,6,7 and similarly, high rates of comorbid pain and PTSD diagnoses have been reported in veterans who have returned from Iraq and Afghanistan.8-10

Context Record numbers of Iraq and Afghanistan veterans survive their war injuries and yet continue to experience pain and mental health problems, particularly posttraumatic stress disorder (PTSD). Little is known about the association of mental health disorders and prescription opioid use.

Objective To investigate the effect of mental health disorders, particularly PTSD, on risks and adverse clinical outcomes associated with prescription opioid use.

Design Retrospective cohort study involving 141,029 Iraq and Afghanistan veterans who received at least 1 non–cancer-related pain diagnosis within 1 year of entering the Department of Veterans Affairs (VA) health care system from October 1, 2005, through December 31, 2010.

Main Outcome Measures Independent association of mental health disorders and the prescription of opioids, higher risk opioid use, and adverse clinical outcomes (eg, accidents and overdose) within 1 year of receiving a pain-related diagnosis.

Results A total of 15,676 veterans were prescribed opioids within 1 year of their initial pain diagnosis. Compared with 6.5% of veterans without mental health disorders, 17.8% (adjusted relative risk [RR], 2.58; 95% CI, 2.49-2.67) of veterans with PTSD and 11.7% (adjusted RR, 1.74; 95% CI, 1.67-1.82) with other mental health diagnoses but without PTSD were significantly more likely to receive opioids for pain diagnoses. Of those who were prescribed pain medication, veterans with PTSD were more likely than those without mental health disorders to receive higher-dose opioids (22.7% vs 15.9%, adjusted RR, 1.42; 95% CI, 1.31-1.54), receive 2 or more opioids concurrently (19.8% vs 10.7%, adjusted RR, 1.87; 95% CI, 1.70-2.06), receive sedative hypnotics concurrently (40.7% vs 7.6%, adjusted RR, 5.46; 95% CI, 4.91-6.07), or obtain early opioid refills (33.8% vs 20.4%; adjusted RR, 1.64; 95% CI, 1.53-1.75). Receiving prescription opioids (vs not) was associated with an increased risk of adverse clinical outcomes for all veterans (9.5% vs 4.1%; RR, 2.33; 95% CI, 2.20-2.46), which was most pronounced in veterans with PTSD.

Conclusion Among US veterans of Iraq and Afghanistan, mental health diagnoses, especially PTSD, were associated with an increased risk of receiving opioids for pain, high-risk opioid use, and adverse clinical outcomes.

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Author Video Interview available at www.jama.com.
in the United States.12–14 Iraq and Afghanistan veterans with pain- and PTSD-prescribed opioids may be at particularly high risk of prescription opioid misuse given the high cooccurrence of substance use disorders among veterans with PTSD.15,16 Despite media reports of overdose in these veterans with pain- and PTSD-prescribed opioids,17,18 little is known about the association of mental health disorders and PTSD with patterns of prescription opioid use and clinical outcomes. We undertook this study in a national sample of Iraq and Afghanistan veterans enrolled in VA health care to investigate the effect of mental health disorders, particularly PTSD, on patterns of opioid prescription, associated risks, and adverse clinical outcomes, such as accidents and overdose.

METHODS

Study Population

This retrospective cohort was identified using the national VA’s OEF/OIF roster, an accruing national database of veterans who have separated from military service and have enrolled in VA health care. Under a waiver of informed consent granted by the institutional review board of record, we identified veterans who entered VA health care from October 1, 2005, through December 31, 2008 (N=291,205). We chose this period to minimize background shifts in opioid prescribing patterns in the VA because the joint VA–Department of Defense clinical practice guideline for the management of opioid therapy was released in 200319 and was not updated until May 2010. The main study population was defined as Iraq and Afghanistan veterans who received a new noncancer-pain diagnosis within 1 year of VA entry (n=141,029). Each veteran was followed up for 1 additional year from initial pain diagnosis to evaluate whether he/she received an opioid prescription and whether he/she experienced an adverse clinical outcome during this 1-year follow-up period. Selecting the subgroup with noncancer pain diagnoses allowed for increased precision with respect to indications for opioid prescription and temporal relationships among variables. The study end-date was December 31, 2010. The study was approved by the Committee on Human Research, University of California, San Francisco, and the San Francisco VA Medical Center.

Data Source

The VA OEF/OIF roster contains basic sociodemographic and military service information but lacks information on income, employment, education, and level of combat exposure and has only crude race/ethnicity categorization.20 The roster data were linked to 2 other VA administrative databases: the VA National Patient Care Database to obtain information on VA clinical visits and associated clinical diagnoses and the VA decision support system to obtain detailed VA pharmacy records.

Study Variables

Dependent Variables. Through medical literature review and consensus of 2 internists and coauthors (K.H.S. and B.E.C.), we identified noncancer diagnoses, using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, that could result in pain serious enough to warrant an opioid medication (eTable 1 available at http://www.jama.com).14,21 We required at least 1 opioid prescription for a minimum of 20 consecutive days in the first year of pain diagnosis. To compare opioid doses across classes, we used a standard formula to calculate morphine equivalents.22 Within 1 year of first pain diagnosis, we determined the following: morphine equivalent dose (in quintiles), median duration of prescription opioid use, and whether 2 or more different opioids, sedative hypnotics (eg, benzodiazepines), or both were prescribed concurrently within a 30-day period. We defined early refill as obtaining the same opioid prescription for more than 7 days before the end of the prior prescription as a proxy of high-risk opioid behavior. Finally, using ICD-9-CM diagnostic codes, we created the following categories of adverse clinical outcomes: (1) accidents resulting in wounds or injuries, (2) opioid-related accidents and overdose, (3) alcohol- and nonopioid drug–related accidents and overdose, (4) self-inflicted injuries (eg, suicide attempt), and (5) violence-related injuries (eg, gunshot wounds) (eTable 2). To ensure the clinical relevance of these outcomes, we required that outcomes occur within 1 year of pain diagnosis in the context of an emergency or inpatient admission and excluded diagnoses received as part of routine, scheduled care.

Independent Variables. We defined 3 mental health diagnostic categories: (1) no mental health diagnoses, (2) other mental health diagnoses excluding PTSD, and (3) PTSD diagnoses with and without other mental health diagnoses. Because the vast majority of individuals with PTSD have comorbid mental health disorders,23 we did not create a separate category of those with PTSD alone. Categories were created using ICD-9-CM codes20 corresponding to Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) classifications.24 We examined other common military service–related mental health diagnoses26: depressive disorders, anxiety disorders, alcohol use disorders, drug use disorders, and traumatic brain injury. Each of these conditions was examined with and without comorbid PTSD. Mental health diagnoses were included that were assigned after entry in VA health care until 1 year after receiving an index pain diagnosis. To adjust for potential confounding, we included sociodemographic (ie, age, sex, race/ethnicity, marital status, VA facility type—medical center vs community clinic) and military service characteristics (ie, component, rank, service branch, and number of deployments).21

Statistical Analyses

For the main study population of 141,029 veterans receiving pain-related diagnoses followed up for 1 year,
In the main study population of veterans with noncancer pain diagnoses (n = 141,029), we performed stratified analyses of subgroups of OEF/OIF veterans with PTSD vs no mental health diagnoses who were prescribed opioids using Mantel-Haenszel tests of homogeneity. Among veterans with pain-related diagnoses prescribed opioids (n = 15,676), we determined independent associations of mental health diagnostic category with prescription opioid-use patterns. Finally, we determined the prevalence of adverse clinical outcomes (defined above) for veterans within each mental health diagnostic category who were and were not prescribed opioids for pain. Because of the extremely large data set, we chose a P value of <.001 as a more conservative threshold for statistical significance. All analyses were conducted using SAS software version 9.1 (SAS Institute Inc).

**RESULTS**

Of 291,205 veterans who entered VA health care from 2005 through 2008, during 1 year of follow-up, 141,029 (48%) received at least 1 pain-related diagnosis. Sociodemographic and military service characteristics of the 141,029 veterans with an index pain diagnosis are presented in Table 1. The majority (66%) had received 2 or more different pain diagnoses; 51% received at least 1 mental health diagnosis—19% received mental health diagnoses excluding PTSD and 32% received PTSD diagnoses with or without other mental health diagnoses.

### Opioid Prescriptions

Of the 141,029 veterans with pain diagnoses, 15,676 (11.1%) received prescription opioids for 20 or more consecutive days; 77% of which were prescribed by VA primary care clinicians. Compared with 6.5% of veterans without a mental health diagnosis, 17.8% (adjusted RR, 2.58; 95% CI, 2.49-2.67) with PTSD and 11.7% (adjusted RR, 1.74; 95% CI, 1.67-1.82) with mental health diagnoses but not PTSD were significantly more likely to receive opioids for pain (Table 2). Similarly, in the whole population of 291,205 veterans with and without pain diagnoses, 12.3% with PTSD (adjusted RR, 4.32; 95% CI, 4.17-4.49) and 7.3% with mental health diagnoses excluding PTSD (adjusted RR, 2.65; 95% CI, 2.54-2.77) were independently more likely to receive opioids than the 2.7% of veterans without mental health diagnoses who received opioids for pain (Table 2). In both cases, the nonoverlapping confidence intervals indicated that veterans with PTSD diagnoses were significantly more likely to be prescribed opioids than veterans with mental health diagnoses other than PTSD.

Stratified analyses confirmed that all subgroups of veterans with PTSD were significantly more likely to receive prescription opioids than those with no mental health diagnoses (Figure). For most subgroups assessed, the confidence intervals around the RRs of being prescribed opioids for veterans with PTSD (vs those with no mental health diagnoses) overlapped with the summary estimate. There was no significant interaction by sex, race/ethnic group, or military rank. There was significant interaction slightly diminishing the effect for veterans younger than 30 years, of active duty service, or former Marines, yet the relationship between PTSD and opioid prescription remained significant (Figure).

Veterans with other specific mental disorder diagnoses—depression, anxiety, alcohol use disorders, drug use disorders, and traumatic brain injury—were significantly more likely to receive opioids than veterans with no mental health diagnoses (eTable 3 available at http://www.jama.com). Of note, veterans with a drug use disorder and comorbid PTSD were most likely to be prescribed opioids than veterans with no mental health disorders (33.5% vs 6.5%; adjusted RR, 4.19; 95% CI, 3.84-4.57; eTable 3). Within each mental disorder diagnosis subgroup, veterans having comorbid PTSD were significantly associated with being at greater risk of receiving prescription opioids than veter-
erans with these diagnoses without co-
morbid PTSD (Table 3).

Higher-Risk Opioid Use
In the 15 676 veterans prescribed opi-
oids within 1 year of initial pain diag-
oses, we detected patterns of higher-
risk opioid use in veterans with mental
health diagnoses other than PTSD, but
especially in veterans with PTSD (Table
4). Compared to veterans without
mental health diagnoses, those with
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related accidents and overdose; self-
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scribed opioids, the absolute risk of all
adverse clinical outcomes, except for
wounds and injuries, was greatest for
the PTSD group than for veterans with-
out a mental health diagnosis or men-
tal health diagnoses other than PTSD
(Table 4).

Adverse Clinical Outcomes
Among the 141 029 veterans followed
up for 1 year after receiving a pain-
related diagnosis, those prescribed opi-
oids (vs not) across all mental health
categories had a higher prevalence of
all adverse clinical outcomes occur-
ring in the context of emergency de-
partment or inpatient admissions (ac-
cidents resulting in wounds or injuries;
opioid-related accidents; and over-
doses, alcohol- and non-opioid drug-
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COMMENT
This is the first national-level study to
demonstrate that veterans of Iraq and
Afghanistan with mental health diag-
oses, particularly PTSD, are signifi-
cantly more likely than veterans with
no mental health diagnoses to receive
prescription opioid medications for

Table 2. Mental Health Diagnostic Category and Receipt of Prescription Opioidsa

<table>
<thead>
<tr>
<th>Mental Health Diagnostic Category</th>
<th>None</th>
<th>Diagnosis Without PTSD</th>
<th>PTSD With and Without Another Mental Health Diagnosis</th>
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<tbody>
<tr>
<td>First year of pain diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of veterans</td>
<td>68737</td>
<td>27309</td>
<td>44983</td>
</tr>
<tr>
<td>No. (%) of opioid prescriptions</td>
<td>4488</td>
<td>6.5 (CI 3205 (11.7) 7983 (17.8)</td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1</td>
<td>Reference</td>
<td>1.80 (1.72-1.88)</td>
</tr>
<tr>
<td>Adjusted RR (95% CI)</td>
<td>1</td>
<td>Reference</td>
<td>1.74 (1.67-1.82)</td>
</tr>
</tbody>
</table>

First year in VA health care system

<table>
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<tr>
<th>Opioid prescriptions, No. (%)</th>
<th>4972 (2.7)</th>
<th>3176 (7.3)</th>
<th>7414 (12.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (95% CI)</td>
<td>2.74 (2.63-2.86)</td>
<td>4.65 (4.49-4.82)</td>
<td></td>
</tr>
<tr>
<td>Adjusted RR (95% CI)</td>
<td>2.65 (2.54-2.77)</td>
<td>4.32 (4.17-4.49)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PTSD, posttraumatic stress disorder; RR, relative risk; VA, Veterans Affairs.

a Adjusted for age, sex, race, marital status, component, rank, branch of service, multiple deployments (y/n), and primary VA facility type.

Although significant for all subgroups, tests for interaction showed that the effect was slightly diminished in veterans who were younger than 30 years, were never married, had enlisted in active-duty service, and were former Marines because these confidence intervals did not overlap with the summary estimate, repre-
sented as the diamond with the width representing the bounds of the summary confidence interval.

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pain-related conditions. The association between PTSD and opioid prescription was robust because it was significant for all subgroups of veterans with PTSD. Moreover, veterans with other mental disorders (eg, substance use disorders and traumatic brain injury) were more likely to receive prescription opioids when PTSD was present as a comorbid diagnosis. Veterans with mental health diagnoses prescribed opioids, especially those with PTSD, were more likely to have comorbid drug and alcohol use disorders; receive higher-dose opioid regimens; continue taking opioids longer; receive concurrent prescriptions for opioids, sedative hypnotics, or both; and obtain early opioid refills. Finally, receiving prescription opioids was associated with increased risk of adverse clinical outcomes for all veterans returning from Iraq and Afghanistan, especially for veterans with PTSD, who were at highest risk of alcohol-, drug-, and opioid-related accidents and overdose, as well as self-inflicted injuries.

A few previous studies have reported a relationship between prescription opioid use and mental health diagnoses.25-27 To our knowledge, only 2 prior studies have focused specifically on the use of analgesic pain medication in outpatients with PTSD.28,29 Both studies found higher rates of prescription opioid use in patients with PTSD, particularly those with the highest PTSD symptom severity scores.28,29 Patients with PTSD have been observed to have dysregulation of the endogenous opioid system through lower pain thresholds and lower endogenous opioid levels.30 Unfortunately, treatment with opioids among patients with mental health problems may result in or exacerbate substance abuse and worsening of mental health symptoms over time.25,31,32 Our results revealed that veterans with PTSD-prescribed opioids for pain used higher doses for longer periods and experienced substantially more adverse clinical outcomes than veterans with other or no mental health disorders.

Veterans with mental health problems, particularly PTSD, have barriers to seeking mental health treatment33 and preferentially use VA primary care.34,35 As in the broader community, most VA primary care clinicians lack specialized training in the management of comorbid pain and PTSD.11 In a recent small study that reported an increase in chronic opioid use in younger combat veterans, 80% of opioids were prescribed in primary care settings,36 consistent with our finding that 77% of opioids were prescribed by VA primary care clinicians. It is possible that in the primary care setting, opioids may be prescribed to treat a poorly differentiated state of mental and physical pain.25 Morasco et al27 demonstrated that in a sample of veterans with multiple pain problems, those with the highest-risk medical and psychiatric comorbidity were the most likely to receive the highest-dose, highest-risk opioid therapy. This paradoxical finding suggests that patient distress can drive potentially inappropriate opioid therapy, perhaps because physicians do not know how else to handle these challenging patients.37

Compared with other Iraq and Afghanistan war veterans, those with PTSD exhibited higher-risk opioid use and adverse clinical outcomes, including injuries and overdose. The prescription of opioids for patients who already abuse or are dependent on drugs and alcohol not only increases risk for abuse of opioids but also increases the risk of central nervous system depression and overdose.14,38 Despite VA guidelines that urge caution in opioid prescribing for persons with substance use disorders, we found that veterans with drug and alcohol use disorders were more likely to be prescribed opioids than veterans with no mental health diagnoses; this was especially true if they also had a comorbid PTSD diagnosis.14,38 In addition, veterans with PTSD had the greatest risk of being prescribed more than 1 opioid simultaneously and sedative hypnotic medication (typically a benzodiazepine) concurrently with opioids. The prescription of benzodiazepines is common in patients with PTSD, despite a lack of evidence for their efficacy.39 Numerous studies have highlighted the risk of overdose from the coprescription of benzodiazepines and opioids; therefore, alternative therapies should be considered for patients with pain and PTSD.80,81

Some limitations must be considered when interpreting the results of this study. Data were obtained from
VA administrative databases that were subject to clerical errors and lacked variables such as socioeconomic status, so our results may have been subject to misclassification and residual confounding. Second, for our main analyses, we selected a population of VA-enrolled returning veterans with pain diagnoses; thus, those results cannot be generalized to all OEF/OIF veterans. When we examined the whole population of these veterans with and without pain diagnoses in VA health care system during the same period, we found that the magnitude of the risk estimates for opioid prescriptions were greater than in our original analyses of veterans with pain diagnoses. This likely occurred because when using the whole population, those with pain diagnoses (who are more likely to receive opioids) were clustered in the PTSD and other mental health diagnostic categories; whereas veterans without pain diagnoses were clustered in the no mental health diagnosis category. This clustering is expected because PTSD is strongly associated with pain and other physical symptoms.\(^{12,43}\) Additionally, veterans with mental health conditions may be more likely to receive pain diagnoses because they have more clinic visits and may appear more distressed about symptoms than veterans without mental health diagnoses.\(^{34}\) We mitigated these potential ascertainment biases by focusing our primary analyses on veterans who had received non-cancer-pain diagnoses.

The index pain diagnosis served as a temporal anchor after which veterans were followed up for an additional year to determine opioid prescriptions and adverse clinical outcomes, thus increasing the precision of our analyses. Nevertheless, our results represent associations between independent and dependent variables and are not evidence of cause and effect. For example, we could not verify patient adherence to opioid prescriptions because pharmacy information was derived from administrative databases. Therefore, we could not be certain that adverse outcomes occurred at the same time veterans were taking prescription opioids; only that the adverse clinical outcome occurred within the same 1-year period as opioid prescription. We could not confirm that mental health disorders, such as PTSD, increased risk for pain and opioid use or misuse because we ascertained mental health diagnoses before

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and after pain diagnoses and opioid prescriptions. We chose this study design because the natural history of postdeployment mental health diagnoses is characterized by delayed onset of symptoms and delayed detection of mental health diagnoses due to patient- and system-level barriers. Considering these limitations, our results demonstrate increased opioid prescriptions, higher-risk opioid use patterns, and increased adverse clinical outcomes associated with opioid use in veterans with pain and mental health diagnoses, particularly PTSD. These findings support further efforts to improve care of patients with comorbid pain and PTSD because of the heightened risk of self-medication with opioids and substance abuse in veterans with PTSD, which may result in further declines in interpersonal and occupational functioning. Trials assessing the efficacy of opioids in treating chronic noncancer pain have shown only modest or equivocal benefit. In contrast, multiple studies have described numerous harms, including overdose death, from the upsurge of opioid prescribing in recent years. Returning combat veterans are presenting to primary care in large numbers and are seeking relief from physical and psychological pain. Extra care should be taken when prescribing opioids to relieve their distress. These patients may benefit from biopsychosocial models of pain care including evidence-based nonpharmacologic therapies and nonopioid analgesics. Integrated treatments that target both mental health disorders and pain simultaneously are effective for both problems and may decrease harms resulting from opioid therapy.

Author Contributions: Dr Seal had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Seal, Neylan, Shi, Krebs, Maguen, G. Cohen, B.E. Cohen. Acquisition of data: Shi. Analysis and interpretation of data: Shi, Seal, Neylan. Drafting of the manuscript: Seal. Critical revision of the manuscript for important intellectual content: Seal, Shi, G. Cohen, B.E. Cohen, Maguen, Krebs, Neylan. Statistical Analysis: Shi. Obtained funding: Seal.

REFERENCES
Mental Health Disorders and Opioid Use in Veterans


