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Opioid Dosing Trends Over Eight Years Among US Veterans with Musculoskeletal Disorders After Returning from Service in Support of Recent Conflicts

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Abstract

Purposes—To examine long-term opioid dosing trends among Veterans with chronic pain.

Methods—We identified 79,015 Veterans with musculoskeletal disorders who were dispensed 1 opioid prescriptions between 2002–2009 after returning from recent conflicts. Opioid dosing trends were examined using a generalized estimating equation while accounting for patient characteristics, temporal and geographic confounding.

Results—In total 472,819 opioid prescriptions were dispensed (mean±standard deviation: 6.0±10.1 per Veteran). Both average daily morphine equivalents (ME/d) and the proportion of high-dose prescribing (>100 ME/d) increased from baseline period (2002–2004) to 2006 then remained relatively stable. Veterans with *extended-persistent* (>40 days over 1–2 episodes) and *extended-intermittent* (>40 days over 3 episodes) dispensing patterns received more high-dose prescriptions than those dispensed prescriptions <40 days, with adjusted Odds Ratios (95% Confidence Interval) of 7.2 (6.0–8.8) and 3.6 (3.0–4.3), respectively. Post-traumatic Stress Disorder and other mental health diagnoses were associated with 30% increased odds of high-dose prescribing.

Conclusions—The average daily dose of opioid prescriptions and the likelihood of high-dose prescribing to these Veterans appeared to increase from 2002–2006 then remained relatively stable

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through 2009. Veterans on opioid prescriptions for extended duration or with mental health diagnoses tend to receive higher dose therapy.

Keywords

opioid dosing trends; Veterans; musculoskeletal pain; electronic pharmacy records; dynamic cohort; dispensing pattern; mental health diagnoses

Introduction

The steady increase in opioid-related adverse events and fatalities in the United States over past decades have been linked to escalating use of prescription opioids for treating chronic non-cancer pain [1–4]. The quadrupling of opioid-related deaths between 1999 and 2010 occurred in parallel with increases in both national sales of prescription opioids [4] and the rate of prescribed opioids at US outpatient visits for chronic musculoskeletal disorders [5]. The mounting evidence of opioid harms has promoted nationwide efforts to improve opioid safety, including guidelines to reduce high-dose prescribing for chronic non-cancer pain [6–8].

Long-term opioid dosing trends may reflect ongoing changes in clinical practice, especially the prescribers' behavior, following policy and guideline changes and pain management and thus provide opportunity to assess potential impact of such population-based strategies, such as the Veterans Affairs (VA) /Department of Defense (DoD) Opioid Therapy Guideline [8]. However, relatively few studies have systematically investigated opioid dosing trends [9–11]. Using insurance claim data from two health insurance plans, Sullivan and colleagues found that the average prescribed morphine equivalent (ME) daily dose remained relatively stable (about 53 ME/d) between 2000–2005 [9]. Recently among Washington State Medicaid patients, authors used linear regression to model the opioid dosing trends aggregated by quarterly time intervals and found stable median dose (37.5 ME/d) between 2006 and 2010, yet the highest percentile dose declined significantly after a 2007 state opioid dosing guideline [10]. In the VA population, Edlund and colleagues examined opioid prescriptions among 1.3 million patients with chronic pain between 2009–2011 and found that the average daily dose (about 21 ME/d) was largely stable over three years [11]. Two other VA studies compared opioid doses between two brief time windows. While one found comparable average morphine equivalents over a 1-year treatment course between 2004 (22.6 ME/d) and 2011 (21.6 ME/d) [12], the other observed significant decrease in both the rate of high-dose opioid prescribing (from 13.7% to 11.0%) and the mean daily dose (from 43 to 23 MED) 90-days before (year 2011) and after (year 2014) implementation of a local Opioid Safety Initiative targeting high-risk prescribing [13]. None of above studies accounted for potential confounding across opioid prescriptions due to heterogeneous patient characteristics, market changes in opioid formularies, or variation in clinical practice across geographic regions.

To fill this knowledge gap, we sought to examine opioid dosing trends in the VA population using data on pharmacy dispensing records between 2002–2009, a time window of potential “exposure” to the VA/DoD guideline that was first released in 2003 and not updated until

2010 [8,20]. We aimed at elucidating opioid dosing trends in both the prescribed daily dose and high-dose prescribing among a dynamic cohort of Veterans with musculoskeletal pain, while simultaneously accounting for potential confounding by Veteran characteristics, temporal and geographical variations across the prescriptions over this extended study period.

Methods

Study Population and Data Sources

Participants were identified from the Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND) roster provided by the Defense Manpower Data Center—Contingency Tracking System Deployment File to the Women Veterans Cohort Study (WVCS) [14]. The roster contained a list of Veterans who deployed in support of OEF/OIF/OND and separated from military service and enrolled for VA health care between September 12, 2002 and July 31, 2010 (N=749,036). Data on opioid dispensing during the study period was abstracted from electronic VA pharmacy records, which include generic name, strength, quantity, route of administration, days' supply and dispensing date. Of the 749,036 Veterans on the roster, 102,486 (13.7%) filled at least one opioid prescriptions at a VA pharmacy during the study period. To facilitate clinical inference and comparison with other opioid trend studies, we restricted study sample to 79,015 Veterans (77.1%) who received a musculoskeletal diagnosis, the most common pain indications for opioid treatment, during two or more outpatient visits within 18 months or one inpatient visit [15] and who did not have a diagnosis for cancer anytime during the study period according to International Classification of Diseases-Ninth Edition (ICD-9) codes. The pharmacy records and electronic health records were obtained from the VA corporate data warehouse (CDW). The study was approved by the VA Connecticut Research and Development Committee (West Haven, CT).

Study Measurement

Outcome measure, average daily dose prescribed and high-dose prescriptions—For each opioid dispensed, average daily dose was calculated based on the quantity, strength, and days' supply, and transformed into average daily morphine equivalents in milligrams (ME/d) using established conversion factors [16,17]. Prescriptions with a ME/d $\geq 1,000$ mg or total number of supply > 90 days were excluded to avoid potential data entry error or implausible outliers [11]. To provide a complete picture of opioid dosing trends, all opioids were included, regardless of duration of action, route of administration, and dosing schedule. To enhance clinical relevance, we also defined a binary outcome for high-dose prescribing based on the prescribed daily dose ≥ 100 ME/d for each dispensed prescription [1,17].

Opioids and corresponding ME conversion factors are listed in Supplementary eTable 1.

Dispensing patterns based on duration and episodes of opioid prescriptions

—To account for heterogeneity of opioid prescriptions with regard to duration and frequency and to compensate for the lack of data on opioid indications, we defined *a priori* dispensing

pattern based on the total duration of all opioid prescriptions and number of prescription *episodes* over entire study period. The duration was the sum of total number of days supplied across all opioid prescriptions; whereas an *episode* referred to serial prescriptions dispensed consecutively with a gap ≥ 14 days. Veterans were divided into three mutually exclusive dispensing patterns based on population median duration and median number of episodes: *limited* (duration <40 days regardless of numbers of episodes), *extended-persistent* (≥ 40 days over 1–2 episodes), and *extended-intermittent* (≥ 40 days over ≥ 3 episodes). Consecutive prescriptions with minimal interruption may be indicated by the same underlying conditions [18] or otherwise reflect patients' persistence on or adherence to the prescribed treatment [19]. Therefore, combining prescription *episode* (instead of prescription) and total prescribed duration may help identify subgroups of Veterans with homogeneous dispensing patterns, who shared underlying indications for opioid prescribing; whereas the *persistent-intermittent* distinction allowed further differentiation of *extended* opioid users with regard to apparent adherence.

Measures of covariates—Demographic characteristics included age, gender, race/ethnicity and education at enrolment in the VA healthcare system, the last military status before retirement (active duty versus national guard or reserve), and >1 deployments (vs 1). To account for heterogeneity of musculoskeletal diagnoses, we defined a binary covariate to identify Veterans with at least one (versus none) of the three most common chronic pain conditions: low back pain, neck pain and osteoarthritis [15].

Since mental health disorders have been associated with increased frequency and duration of opioid use [11–13,15,20], we selected three common mental health diagnoses as individual risk factors, including post-traumatic stress disorders (PTSD), major depressive disorders (MDD) and substance use disorders (SUD) (Supplementary eTable 2 shows a complete list of ICD-9 codes). Other clinical covariates were defined globally, using the Charlson Comorbidity Index (≥ 1 versus 0) for overall physical health and a binary indicator for having ≥ 1 other psychiatric diagnoses (including anxiety disorders, minor depression, bipolar disorder, schizophrenia, schizoaffective disorders and psychosis not otherwise-specified, based on ICD9-CM codes). Pain intensity was documented on a 10-point numerical rating scale [15]. Finally, we calculated number of days elapsed from baseline to the index musculoskeletal diagnosis, the first opioid prescription dispensed and the first VA primary care visit, respectively, and used the Veteran Integrated Service Networks (VISN) regions where Veterans obtained their index musculoskeletal diagnoses, to capture the temporal variation or geographic heterogeneity of the opioid prescriptions [12,17,21–23].

Statistical Analyses

Baseline characteristics and t measures of opioid prescriptions were summarized using frequency (percentages) and means ($\pm$ standard deviations (SD)) or medians (intra-quartile Range (IQR)), as appropriate, for the whole sample and according to dispensing patterns. The annualized average daily dose (ME/d) was calculated by dividing the aggregated total doses across all person-prescriptions dispensed by total number of days supplied in a given year. Due to limited number of prescriptions (9,840 in total), years 2002–2004 were collapsed into a single baseline period for annual trend analyses.

We used a general estimating equation (GEE) [24,25] to model the complete dispensing history over the eight-year study period, with individual person-prescriptions as the analytic unit. Each Veteran can contribute more than one observations to the analyses each time when they filled a prescription, as if entering and exiting an open (or *dynamic*) cohort multiple times [26]. This person-prescription based analysis allowed depicting the dynamic course of opioid prescribing over an extended time period, in which both the recipients who were dispensed opioid prescriptions and the number of prescriptions dispensed varied substantially from one year to the next (See Tables 2 and 3 below).

To model the average daily dose prescribed, we used a log-transformed ME/d as a normal outcome to account for the skewness of the original ME/d scale. After inspecting the average ME/d over each calendar year and exploring time effects using dummy indicators, we decided to use a linear and a quadratic term to capture potential nonlinear dosing trends over six calendar intervals from 2002–2004 to 2009. In the primary analyses, we first fit a baseline, time-trends only GEE normal model of log (ME/d) by including only the linear and quadratic terms for the ordinal calendar years and the predefined dispensing patterns. The derived parameter estimate for the linear time (βt) therefore represents *absolute change* in the log (ME/d) per 1-year increment from years 2002–2004 to year 2009, which can be translated approximately to *percent* change in the original ME/d scale; while the quadratic time (βt^2) determines the speed and direction of predicted annual change, with a negative βt^2 indicating a later reflection of initial ascending [27]. The parameter estimates for a dummy variable (e.g., the dispensing patterns) denotes *absolute difference* on log (ME/d) (approximately, percent difference in original ME/d) between Veterans in an index category (e.g., *extended-persistent* or *extended-intermittent*) versus those in the reference category (e.g., the *limited* pattern).

Next, we introduced PTSD, MDD and SUD into the baseline model as individual binary covariates, along with other potential confounding, including demographics, active duty status, > 1 deployment, CCI > 1, low back pain, neck pain and/or osteoarthritis diagnoses, 1 other psychiatric diagnoses; time to first opioid and dummy indicators for 21 VISN regions. Correlation among serial prescriptions dispensed to the same Veteran over time was accounted for using a first-order autoregressive covariance structure. Model fit was inspected using the Quasi-Information Criterion and residual plots.

In secondary analyses, we fit a GEE logistic model of high-dose prescribing (≥ 100 vs <100 ME/d) as a binary outcome, with and without adjusting for the same set of covariates as the GEE normal models above. The derived parameter estimates for calendar years represent predicted change in log (odds) of high-dose prescribing per-1 year increment (linear time), offsetting an accelerated increase or decrease in the predicted annual change over time (quadratic time) [27]; whereas the effect estimates for the dispensing patterns (and other dummy variables) can be conveniently exponentiated to odds ratios (OR) to facilitate clinical interpretation.

We performed sensitivity analyses to examine the robustness of the final models. Tramadol, an atypical opioid analgesic with a maximum dose of 40 ME/d, was introduced into VA in 2004 and was the second most commonly dispensed opioid during the study timeframe (see

Supplementary eTable 1). To determine whether tramadol explained the overall opioid dosing trend, we refit GEE-normal models and the GEE-logistic models by eliminating all tramadol prescriptions (114,005 records). Next, for the adjusted GEE normal model only, we (1) introduced baseline Body Mass Index (BMI) as an additional covariate (N=77,369); (2) restricted analyses to those with a baseline pain intensity score ≥ 4 (N=38,432), indicative of moderate to severe pain [15,28]; and (3) restricted the analyses to those who filled first opioid prescriptions within 3 months of the index musculoskeletal diagnoses (N=33,968). In addition, to determine whether the apparent opioid dosing trends were driven by changing clinical characteristics of the study cohort over time, we refit final models by excluding Veterans with PTSD (N=38,948), the most common mental health diagnoses associated with high-dose opioid prescribing in this study. Finally, we refit the GEE-logistic model using ME/d ≥ 180 as an alternative outcome for high-dose prescribing.

All statistical analyses were conducted using SAS software version 9.3 (SAS Institute, Cary NC 2010). Hypotheses were tested at a two-sided significance level of $\alpha = 0.05$.

Results

As shown in Table 1, the average age was 30 years (Range: 18–62 years), with most male (89%), white (66%) and high school or higher education (84%). The most common mental health diagnosis was PTSD (49%), followed by SUD (19%) and MDD (16%), with 23% of Veterans having two or three such conditions. The prevalence of common musculoskeletal diagnoses was 50% for lower back pain, 30% for neck pain and 20% for osteoarthritis, with two thirds of Veterans having at least one conditions. In comparison to the excluded Veterans (N=23,471), the study sample was younger (29.8 ± 9.1 vs 30.1 ± 10.1 years), had fewer women (11.4% vs 16.0%) and non-white race (34.4% vs 35.4%), yet higher prevalence of PTSD (49.3% vs 31.3%) and MDD (16.0% vs 11.4%).

During the eight-year study period, 472,819 opioid prescriptions were dispensed. The most commonly dispensed opioid was hydrocodone (41.3%), followed by tramadol (24.1%) and oxycodone (16.2%) (See Supplementary eTable 1).

As summarized in Table 2, on average each Veteran was dispensed six opioid prescriptions over 2.5 episodes, for a total duration of 133.7 ± 230.5 days. Most Veterans obtained their initial musculoskeletal diagnoses (median: 693 days) and their first opioid prescriptions (median: 712 days) more than one year after returning from conflicts.

As shown in Table 3, the annualized average ME/d per prescription increased from 2002–2004 (25.5) to 2006 (29.8), then stayed relatively stable from 2007–2009 (29.9, 29.9 and 30.1). The proportion of high-dose prescriptions dispensed within each year increased from 1.7% in 2002–2004 to 2.9% in 2006, then stayed relatively stable (2.9%, 3.1% and 2.9%, respectively).

The *extended-intermittent* (28.7 ± 35.0) and *extended-persistent* (35.6 ± 45.1) recipients had higher ME/d than the *limited* recipients (23.7 ± 19.7), and a greater proportion of high-dose prescriptions (2.5%, 5.2% versus 0.5%).

Table 4 summarizes the GEE model results. The adjusted model of log (ME/d) estimated a significant linear ($\beta t = 0.03$, $p < 0.001$) and significant quadratic ($\beta t^2 = -0.003$, $p = 0.001$) annual changes from 2002–2004 to 2009, suggesting an initial escalating dosing curve bended around 2006 followed by a plateau. The odds of high-dose prescribing followed a similar curve-linear trend ($\beta t = 0.12$, $p = 0.012$; $\beta t^2 = -0.02$, $p = 0.018$). These predicted dosing trends largely agreed with the observed annualized average doses over the eight years shown in Table 3.

Relative to those dispensed *limited* prescriptions, Veterans with the *extended-persistent* dispensing pattern had both higher log (ME/d) dose (adjusted mean difference: 0.059; 95% CI: 0.043–0.075), and greater odds of high-dose prescribing (adjusted OR: 7.24; 95% CI: 5.95–8.81); those with the *extended-intermittent* pattern had an increased OR of high-dose prescribing (adjusted OR: 3.56; 95% CI: 2.96–4.28), but comparable average daily dose ($p = 0.232$). Veterans with PTSD, MDD or SUD had both higher log (ME/d) dose (adjusted mean difference: 0.038, 0.057, 0.063; all p values < 0.0001) and greater odds of high-dose prescribing (adjusted OR, 1.31; 1.36; 1.32; $p = 0.008$, 0.001, 0.002) than those without each diagnosis, respectively. In addition, both the average daily dose and the odds of high-dose prescribing varied across the 21 VISN regions (Type 3 tests, $df = 20$; $p < 0.001$; $p = 0.006$, respectively).

Eliminating tramadol prescriptions derived consistent results. The curvilinear dosing trends were retained with both the GEE-normal model of log (ME/d) dose ($p < 0.0001$ for both βt and βt^2) and the GEE-logistic model of high-dose prescribing ($p = 0.014$ for βt ; $p = 0.030$ for βt^2). Similarly, the *extended-persistent* dispensing pattern and the three mental health diagnoses were each associated with an increased average log (ME/d) dose and increased odds of high-dose prescribing (Supplementary eTable 3).

In additional sensitivity analyses (Supplementary eTable 4), curvilinear trends of average log (ME/d) dose remained significant (models 1–3), as did the adjusted associations of high-dose prescribing with dispensing patterns (*extended-intermittent*, *extended-persistent* vs *limited*) and the three mental health diagnoses. These associations became stronger when the analyses were restricted among Veterans with moderate to severe pain (model 2) or those who filled first opioid prescriptions within 3 months of initial musculoskeletal diagnoses (model 3). Excluding Veterans with a diagnosis of PTSD did not change the predicted dosing trends of the average log (ME/d) ($\beta t = 0.03$, $p < 0.001$; $\beta t^2 = -0.003$, $p = 0.013$) or the odds of high-dose prescribing ($\beta t = 0.19$, $p = 0.035$; $\beta t^2 = -0.03$, $p = 0.060$). Refitting the adjusted GEE-logistic model of high-dose prescribing by ME/d 180 derived comparable results (data available upon request).

Discussion

Our study suggests that prescribed opioid dosing during the study period did not follow the same trend as the total volume of opioid prescriptions among Veterans with musculoskeletal pain. Although the overall numbers of opioid prescriptions and total numbers of recipients both escalated each year from 2002–2009, the prescribed daily dose and the proportion of high-dose prescriptions dispensed did not. In fact, an increasing dosing was apparent only up

to year 2006. Thereafter both the prescribed daily dose and the proportion of high-dose prescriptions appeared to level off and remained relatively stable through 2009. This may have two important public health implications.

First, the increasing dosing trend from 2002–2006 seems unique to the existing literatures [9,11,12], yet paralleled the national trends of escalating opioid prescriptions for chronic non-cancer pain during that period, when more liberal standards for pain management, increasing awareness of the patients' right to pain relief and aggressive marketing by the pharmaceutical industry were witnessed [2,4,9,10]. Second, the levelling of dosing trends between 2006 and 2009 provides partial support for a relatively stable opioid prescribing practice during the same or subsequent time periods observed in the VA populations [11,12,13]. Our study extended those previous literatures with more thorough control of person-specific, temporal and geographic confounding. Interestingly, our study period was temporally preceded by the launch of the first VA\DoD guideline in March 2003 on management of opioid therapy for chronic pain [8], whose position largely echoed the joint statement by twenty-one health organizations and the Drug Enforcement Administration (AAFP et al 1996–2002) advocating opioid therapy “for moderate to severe pain that has failed other therapeutic intervention” [8]. We demonstrated the changing dosing trend cannot be explained by the VA formulary change in 2004 introducing tramadol, or by changing clinical characteristics of the study cohort over time, especially with regard to PTSD diagnosis. More studies are needed to clarify whether and to what extent this potential prescribing practice change may reflect the VA policy impact, a broader shift in the opioid prescribing philosophy in the nation, or increasing awareness among VA prescribers to the risks of chronic opioid treatment for non-cancer pain [11].

Strengths of this study includes a large sample of Veterans and an extended post-deployment follow-up period, offering a unique opportunity to examine the long-term opioid dosing trends. In addition, directly modeling person-prescriptions, instead of persons or person-times, allowed us to optimally utilize the comprehensive VA pharmacy records and reduce potential selection bias and measurement errors. Furthermore, by simultaneously accounting for a large array of patient characteristics, along with covariates capturing the temporal and geographical heterogeneity across opioid prescriptions, we mitigate potential “ecological fallacy” that faces time- or space-aggregated population studies due to lack of control for individual-level covariates [26,29]. Towards this end, our findings that Veterans who were dispensed opioids for extended duration or who had a mental health diagnoses tend to receive high dose therapy are highly consistent with existing literatures and offer some validity reassurance [4,11,12,20–23,30].

The limitations of the study include the uncertainty about the indications, actual use and adherence to the dispensed prescriptions by these Veterans. In addition, our observations were based on cumulative morphine equivalents across all opioid prescriptions regardless of dose form, routes of administration or specific analgesic indications. We also did not distinguish between short-acting and long-acting forms of an opioid. Furthermore, our analyses focused on a serial person-prescriptions dispensed to a dynamic cohort over several years, rather than tracing a closed inception cohort longitudinally. Finally, our study included only Veterans of recent conflicts below age 62 years and may not apply to older

Veterans or those with distant combat experience. Therefore, despite of rigorous control of person-specific and temporal-spatial confounding, the time trends reported here must be interpreted in the context of other epidemiological and clinical data.

To conclude, we have documented a potential practice change in opioid prescribing between 2002–2009 among US Veterans with musculoskeletal pain after returning from recent conflicts, with an escalating dose up to 2006 followed by a plateau, independent of individual, temporal and geographic confounding. This changing dosing trend may mirror a dynamic transition in the VA history of opioid prescribing practice towards a less liberal attitude, possibly resulting from constant interplay between the system-wise VA policy implementation and knowledge-based precaution of practicing VA physicians. Future epidemiological studies are warranted to trace subsequent changes in the opioid prescribing practice after the 2010 update of the VA/DoD guideline and the 2014 release of the VA national Opioid Safety Initiatives, and to assess potential impact of opioid dosing trends on clinical outcomes and effectiveness of emerging intervention programs targeting high-risk opioid prescribing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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See Statistical Analyses and Results for model specification details

- This study examined dispensing history of opioid prescriptions among 79,015 US Veterans of recent conflicts with musculoskeletal pain and found an escalating daily dose and high-dose prescribing from 2002 to 2006 followed by a plateau through 2009 after accounting for individual, temporal and geographic confounding.
- Veterans who were dispensed opioid prescriptions for extended duration tend to receive higher average daily dose and greater number of high-dose prescriptions.
- Veterans with a diagnosis of posttraumatic stress disorders, major depressive disorders or substance use disorders were associated with higher dose therapy.

Table 1

Baseline characteristics of 79,015 US veterans with musculoskeletal disorders after returning from recent conflicts, 2002–2009

Characteristics	Overall N=79,015	Dispensing Pattern¶¶		
		Limited N=39,342	Extended-intermittent N=23,833	Extended-persistent N=15,840
<u>Demographics</u>				
Age (yr), mean ± SD	29.8 ± 9.1	29.1 ± 9.0	31.0 ± 9.4	29.8 ± 9.0
<25	31,921 (40.4)	17,465 (44.4)	8,148 (34.2)	6,308 (39.8)
25-	40,338 (51.1)	18,864 (48.0)	13,208 (55.4)	8,266 (52.2)
45-	6,756 (8.6)	3,013 (7.7)	2,477 (10.4)	1,266 (8.0)
Female	9,009 (11.4)	4,954 (12.6)	2,620 (11.0)	1,435 (9.1)
Nonwhite race/ethnicity	27,140 (34.3)	14,301 (36.4)	8,091 (34.0)	4,748 (30.0)
Education above high school	12,452 (15.8)	6,292 (16.0)	3,746 (15.7)	2,414 (15.2)
Currently married	36,268 (45.9)	16,250 (41.3)	12,448 (52.2)	7,570 (47.8)
<u>Military services</u>				
Component				
-Active duty	45,607 (57.7)	22,772 (57.9)	13,390 (56.2)	9,445 (59.6)
-Reserve or Guard	33,408 (42.3)	16,570 (42.1)	10,443 (43.8)	6,395 (40.4)
Number of deployments>1	26,377 (33.4)	13,492 (34.3)	7,588 (31.8)	5,297 (33.4)
<u>Musculoskeletal disorders</u> *				
Lower back pain	39,422 (49.9)	15,310 (38.9)	15,285 (64.1)	8,827 (55.7)
Neck pain	23,734 (30.0)	9,226 (23.5)	9,590 (40.2)	4,918 (31.1)
Osteoarthritis	16,064 (20.3)	5,442 (13.8)	7,220 (30.3)	3,402 (21.5)
Any above diagnoses	49,489 (66.4)	21,851 (55.5)	19,214 (80.6)	11,424 (72.1)
<u>Mental heather diagnoses</u>				
PTSD†	38,945 (49.3)	16,025 (40.7)	14,623 (61.4)	8,297 (52.4)
Major depressive disorders	12,612 (16.0)	4,763 (12.1)	5,457 (22.9)	2,392 (15.1)
Substance use disorders‡	14,951 (18.9)	6,235 (15.9)	5,550 (23.3)	3,166 (20.0)
Other psychiatric conditions¶	10,941 (13.9)	4,013 (10.2)	4,665 (19.6)	2,263 (14.3)
1 other comorbidities§	3,167 (4.0)	1,465 (3.7)	1,145 (4.8)	557 (3.5)
Previous history of opioid prescription¶¶	2,234 (2.8)	875 (2.2)	830 (3.5)	429 (3.3)

Values represent Mean±SD or N (%) for overall sample and according to the three chronicity patterns, with percentage (%) denoting subgroups with each characteristic present.

^{*} Included one or more encounters of ICD9-CM codes for musculoskeletal disorders (MSD) diagnoses, as defined in Methods. Any other MSD diagnoses

[†] Included one or more encounters of ICD9-CM codes for Post-traumatic Stress Disorders (PTSD).

[‡] Included one or more encounters of ICD9-CM codes for alcohol or drug abuse or substance use disorders.

[¶] Included one or more encounters of ICD9-CM codes for anxiety disorders, minor depression, bipolar disorder, schizophrenia, schizoaffective disorders, and psychosis not-otherwise-specified.

[§]Based on Charlson Comorbidity Index.

[#]Based on a pharmacy record of filling one or more opioid prescriptions up to three years before separation from the military service after deployment in OEF/OIF/OND.

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Table 2

Dispensing history of opioid prescriptions among 79,015 US veterans with musculoskeletal disorders after returning from recent conflicts, 2002–2009

	Overall Sample	Dispensing Pattern		
	N=79,015	Limited N=39,342	Extended-intermittent N=23,833	Extended-persistent N=15,840
<i>Total number of opioid prescriptions dispensed</i>	6.0 ± 10.1	1.4 ± 0.8	13.0 ± 13.1	6.8 ± 10.9
<i>Total number of prescription episodes*</i>	2.5 ± 2.4	1.3 ± 0.6	5.3 ± 2.8	1.6 ± 0.5
<i>Total duration (days) supplied opioid†</i>	133.7 ± 230.5	17.7 ± 11.0	304.7 ± 297.3	164.5 ± 231.0
<i>Time (days) to initial musculoskeletal diagnosis‡</i>	693 (313–1253)	678 (301–1231)	705 (322–1317)	709 (333–1234)
<i>Time (days) to first opioid prescription‡</i>	712 (356–1196)	766 (373–1292)	624 (318–1024)	750 (389–1232)
<i>Time (days) to first VA primary care visit‡§</i>	385 (148–751)	364 (139–751)	383 (152–714)	436 (171–811)
<i>Total number of days under VA healthcare</i>	1276 (811–1777)	1161 (701–1694)	1553 (1132–1965)	1077 (687–1579)

Values represent Mean±SD or Median (Intra-Quartile range).

* An episode refers to consecutive opioid prescriptions without elapsing more than 14 days between adjacent prescriptions (see Methods for details).

† Based on the days of supply across all opioid prescriptions dispensed during the follow-up period, excluding overlapping between consecutive prescriptions.

‡ Calculated as number of days elapsed from the date of separation from military services after returning from the last deployment, to the date of obtaining initial diagnosis of musculoskeletal disorders, the date of dispensing first opioid prescription, or the date of first VA healthcare visit, respectively.

§ Excluded 934 persons with missing date of VA primary care visit.

Table 3

Average daily morphine equivalents (ME/d) prescribed and proportion of high-dose prescriptions among 79,015 US veterans with musculoskeletal disorders after returning from recent conflicts, 2002–2009

Calendar years	Number of Prescriptions Dispensed [*]	Average ME/d (mg), Mean±SD	High-dose Prescriptions [†] (%)
2002–04	9,840	25.5 ± 24.3	1.6
2005	25,597	27.6 ± 33.4	2.3
2006	50,582	29.8 ± 40.8	2.9
2007	89,774	29.9 ± 38.4	3.1
2008	144,911	29.9 ± 35.7	2.9
2009	152,115	30.1 ± 35.5	2.9
Overall	472,819	29.7 ± 36.4	2.9

^{*} Denominator for calculating mean dose and proportion for each calendar year.

[†] Defined as prescriptions with ME/d ≥ 100 mg.

Table 4

Longitudinal trends and predictors of prescription opioid dosing among 79,015 US Veterans with musculoskeletal disorders after returning from recent conflicts: 2002–2009.

Parameter	GEE Normal Model of Average Daily Dose [*]		GEE Logistic Model of High-dose Prescribing [†]	
	Baseline Model [‡]	Adjusted Model [§]	Baseline Model [‡]	Adjusted Model [§]
<u>Time trend over calendar years[¶]</u>				
<i>Linear term</i>	0.03 (0.02–0.04)	0.03 (0.02–0.05)	0.06 (–0.03–0.15)	0.12 (0.03–0.22)
<i>Quadratic term</i>	–0.003 (–0.005– –0.001)	–0.003 (–0.005– –0.001)	–0.01 (–0.02–0.003)	–0.02 (–0.03– –0.003)
<u>Dispensing pattern[¶]</u>				
<i>Extended-persistent</i>	0.10 (0.09–0.12)	0.06 (0.05–0.08)	2.22 (2.03–2.41)	1.98 (1.78–2.98)
<i>Extended-episodic</i>	0.07 (0.06–0.08)	0.01 (–0.01–0.02)	1.69 (1.51–1.87)	1.27 (1.08–1.45)
<i>Limited (reference)</i>	0.00	0.00	1.00	1.00
<u>Mental health diagnoses[¶]</u>				
<i>PTSD present (vs absent)</i>	N/A	0.04 (0.03–0.05)	N/A	0.27 (0.07–0.46)
<i>MDD present (vs absent)</i>	N/A	0.06 (0.04–0.08)	N/A	0.31 (0.13–0.49)
<i>SUD present (vs absent)</i>	N/A	0.06 (0.05–0.08)	N/A	0.28 (0.11–0.46)

Abbreviations: GEE, Generalized Estimating Equation; PTSD, Post-traumatic stress disorders; MDD, Major depressive disorders; SUD, Substance use disorders; CI confidence intervals; N/A, Not applicable.

^{*} Estimated using a GEE model of average daily dose per prescription in log (ME/d) scale as a normal outcome, with a first-order autoregressive structure to account for within-subject correlations between repeated prescriptions over time.

[†] Estimated using a GEE logistic model of high-dose prescribing (ME/d ≥ 100 mg) as a binary outcome, with a first-order autoregressive structure to account for within-subject correlations between repeated prescriptions over time.

[‡] Included only the linear and quadratic terms for calendar year and two dummy indicators representing the dispensing patterns.

[§] Adjusted for age, female, education above high school, non-white race, component of services (active versus others), having a common musculoskeletal diagnosis (lower back pain, neck pain and/or osteoarthritis), 1 comorbidities and 1 other psychiatric diagnoses; number of months from baseline to first opioid prescription; and 23 Veteran Integrated Service Networks (VISN) sites.

[¶] Values are parameter estimates (95% CI) derived from each GEE model, representing the predicted change in the log(ME/d) or in the predicted log odds of high-dose prescribing, respectively, per 1-year increment in calendar year (2002–04 to 2009).

[¶] Values are parameter estimates (95% CI) derived from each GEE model, representing the predicted absolute difference in the log(ME/d) or in the predicted log odds of high-dose prescribing, respectively, between veterans with and without each predictor.