Overdose Risk for Veterans Receiving Opioids From Multiple Sources

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ABSTRACT

OBJECTIVES: The aim of this study was to evaluate whether veterans in Massachusetts receiving opioids and/or benzodiazepines from both Veterans Health Administration (VHA) and non-VHA pharmacies are at higher risk of adverse events compared with those receiving opioids at VHA pharmacies only.

STUDY DESIGN: A cohort study of veterans who filled a prescription for any Schedule II through V substance at a Massachusetts VHA pharmacy. Prescriptions were recorded in the Massachusetts Department of Public Health Chapter 55 data set.

METHODS: The study sample included 16,866 veterans residing in Massachusetts, of whom 9238 (54.8%) received controlled substances from VHA pharmacies only and 7628 (45.2%) had filled prescriptions at both VHA and non-VHA pharmacies ("dual care users") between October 1, 2013, and December 31, 2015. Our primary outcomes were nonfatal opioid overdose, fatal opioid overdose, and all-cause mortality.

RESULTS: Compared with VHA-only users, more dual care users resided in rural areas (12.6% vs 10.6%), received high-dose opioid therapy (26.3% vs 7.3%), had concurrent prescriptions of opioids and benzodiazepines (34.8% vs 8.2%), and had opioid use disorder (6.8% vs 1.6%) (P <.0001 for all). In adjusted models, dual care users had higher odds of nonfatal opioid overdose (odds ratio [OR], 1.29; 95% CI, 0.98-1.71) and all-cause mortality (OR, 1.66; 95% CI, 1.43-1.93) compared with VHA-only users. Dual care use was not associated with fatal opioid overdoses.

CONCLUSIONS: Among veterans in Massachusetts, receipt of opioids from multiple sources was associated with worse outcomes, specifically nonfatal opioid overdose and mortality. Better information sharing between VHA and non-VHA pharmacies and prescribers has the potential to improve patient safety.

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Concomitant use of opioids with benzodiazepines significantly increases the risk of adverse outcomes. Specifically, rates of overdose death among those who were codispensed benzodiazepines and opioid analgesics were 10 times higher than among those who were dispensed opioid analgesics alone in a prospective cohort study.[1] Similarly, among veterans using opioids, coprescribing of benzodiazepines was associated with an increased risk of opioid-related overdoses, injuries, and mortality.[2] In another veteran-based study, nearly half of drug overdose deaths occurred among those concurrently prescribed benzodiazepines and opioids.[3] Effective prescription monitoring programs (PMPs) have been shown to change such prescriber behavior by bringing about a reduction in opioid prescribing.[4] Robust PMPs, as measured by assessing local and federal laws for prescribing controlled substances, have shown to be associated with fewer opioid overdose deaths than weaker PMPs.[5] However, strong laws cannot overcome fragmented or uncoordinated care, which can still be a barrier to the effective use of PMPs.

Fragmented care results in increased medical errors, hospital readmissions, emergency department (ED) visits, and healthcare costs.[6,7] Specifically, this holds true in the area of pain management, where the risk of opioid misuse may be compounded when patients obtain opioid prescriptions from multiple prescribers and/or pharmacies.[8-10] Such fragmented or uncoordinated care has been shown to be associated with adverse opioid-related outcomes, including hospital admissions associated with opioid use[11] and increased risk of opioid overdose.[12]

The impact of care coordination on opioid-related outcomes has not been fully examined among veterans who have "dual care use" of pharmacy benefits both within and outside of the Veterans Health Administration (VHA).[13,14] Veterans may have a higher risk of overdose given their prevalence of chronic pain disorders, which are often treated with opioids,[15,16] and that risk might be further aggravated with the coprescribing of benzodiazepines.

A recent cross-sectional study using the Kentucky PMP found that compared with those with VHA payments only, veterans with multiple payment sources for opioid prescriptions were more likely to receive risky opioid therapy, defined as combination

opioid/benzodiazepine or high-dose opioid therapy.[17] Besides the fact that it did not examine whether veterans were more likely to experience adverse events, the study also examined VHA as a payer, whereas our current study examines it as a dispenser.

Here, we fill this void in the literature by reporting on whether Massachusetts veterans receiving opioids and/or benzodiazepines from VHA and non-VHA pharmacies are at higher risk of nonfatal opioid overdose, fatal opioid overdose, or all-cause mortality compared with those receiving these prescriptions from VHA pharmacies only. Further, we report on whether risk is associated with the number of transitions between VHA and non-VHA systems.

TAKEAWAY POINTS

Fragmented coordination of care has been shown to be associated with adverse opioid-related outcomes.

- The present study suggests that veterans receiving opioids at both Veterans Health Administration (VHA) and non-VHA pharmacies are at higher risk of opioid overdoses compared with veterans receiving prescriptions at VHA pharmacies only.
- Findings have implications for patient safety and the Veterans Choice program, which offers services from non-VHA providers to veterans living outside of VHA catchment areas.
- Managed care decision makers should query the dual use of pharmacy services—specifically with regard to opioids—in their systems of care and its association with opioid overdoses.

METHODS

The study was conducted on a cohort of veterans with opioid and/or benzodiazepine prescriptions recorded in the Massachusetts Department of Public Health (MDPH) Chapter 55 data set.

Data Source

Chapter 55 Acts of 2015 mandated the analysis of data from several Massachusetts government agencies to report trends on fatal and nonfatal opioid overdoses. The database included 16 administrative sources covering approximately 98% of the Massachusetts population 11 years and older. In our study, we used 6 data sets: PMP, Massachusetts All-Payer Claims Database (APCD), Acute Care Hospital Case Mix Database, death records, Massachusetts Ambulance Trip Record Information System, and Office of the Chief Medical Examiner toxicology data. The PMP maintains information on filled prescriptions for Schedule II through V controlled substances from Massachusetts clinics, hospitals, and retail pharmacies, including out-of-state deliveries to Massachusetts residents. It also includes prescriptions by mail order pharmacies that deliver to patients residing in Massachusetts. Our study data span from October 2013, when VHA data were first systematically reported to the PMP, until December 2015. Other VHA data beyond those reported to the PMP (eg, demographics, diagnosis codes, laboratory test results, or pharmacy records) were not available to us because they have not been linked to the Chapter 55 data sets. The Chapter 55 initiative was mandated by law and conducted by a public health authority. No institutional review board (IRB) review was required by MDPH, and it was deemed exempt from research review by the Bedford VA Medical Center IRB.

Cohort Eligibility Criteria

We defined a veteran as anyone filling a prescription for any Schedule II through V substance at a Massachusetts VHA pharmacy (19,479 veterans). Prescriptions for Massachusetts residents filled outside the state were not included. Further, those with a non-Massachusetts residential zip code (n = 201) or insufficient prescription data to ascertain dual care status (n = 2412) were excluded, resulting in a sample of 16,866 veterans. No veterans were excluded due to age, race, or gender.

Primary Independent Variable

Veterans were categorized into those filling prescriptions for opioids and/or benzodiazepines at VHA pharmacies only ("VHA-only"; n = 9238) or those filling such prescriptions at both VHA and non-VHA pharmacies ("dual care users"; n = 7628). Opioids used for medication-assisted therapy for opioid use disorder, such as buprenorphine, were included (**eAppendix Table** [eAppendix available at **ajmc.com**]). For veterans with dual care use, we quantified the number of switches between VHA and non-VHA fills as a measure of the extent of discoordination in the patients' care. The index date was defined as the earliest date during the study period that a veteran filled an opioid or benzodiazepine prescription, whether inside or outside of the VHA.

Outcomes

We examined 3 outcomes after the index prescription date: nonfatal opioid overdose, fatal opioid overdose, and all-cause mortality. Nonfatal overdose was identified in 2 ways. First, any individual who had an ambulance encounter related to opioid overdose was included. The algorithm that was used to identify opioid-related overdoses in the emergency medical system data was the result of collaboration between MDPH and the CDC.[18,19] The second was an ED visit, outpatient observation, or inpatient hospital discharge with an *International Classification of Diseases, Ninth Revision* code containing a diagnosis code for opioid poisoning. Fatal opioid-related overdoses were defined using the *International Classification of Diseases, Tenth Revision* codes for mortality. These multiple cause-of-death fields were then used to identify an opioid-related death. All-cause deaths were identified using death certificates that are filed with the Massachusetts Registry of Vital Records and Statistics and contain the official cause of death and manner of death assigned by physicians and medical examiners. All outcomes were chronologically sequenced to ensure that none occurred before the index opioid use date.

Covariates

Covariates included age, gender, high-dose opioid therapy (defined as exceeding 50 morphine milligram equivalents per day, on average,

TABLE. Patient Characteristics of the Sample, Massachusetts, 2013-2015

	Filled Prescriptions at VHA Pharmacies Only	Filled Prescriptions at Both VHA and Non-VHA Pharmacies[a]
	n = 9238	n = 7628
Age groups, years, n (%)		
<40	1246 (13.5)	796 (10.4)
40-59	2255 (24.4)	1827 (24.0)
60-79	4568 (49.5)	3708 (48.6)
>80	1169 (12.7)	1297 (17.0)
Female, n (%)	593 (6.4)	522 (6.8)[b]
Nonwhite race/ethnicity, n (%)	618 (6.7)	534 (7.0)
Rural residence, n (%)	977 (10.6)	958 (12.6)
High-dose opioid therapy (>50 MME), n (%)	676 (7.3)	2003 (26.3)
Concurrent opioid and benzodiazepine prescriptions, n (%)	753 (8.2)	2652 (34.8)
At least 1 prescription for buprenorphine, n (%)	263 (2.9)	398 (5.2)
Number of switches between VHA/non-VHA pharmacies, mean (SD)	–	4.8 (8.3)
Rural pharmacy, last fill, n (%)	211 (2.3)	533 (7.0)
Elixhauser physical comorbidity index, mean (SD)	1.3 (2.5)	3.0 (3.8)
Elixhauser mental comorbidity index, mean (SD)	0.2 (0.6)	0.6 (1.0)
Opioid use disorder, n (%)	148 (1.6)	520 (6.8)
Homeless, n (%)	63 (0.7)	111 (1.5)
Nonfatal overdose, n (%)	114 (1.2)	160 (2.1)
Nonfatal overdose events, mean (SD)	0.019 (0.21)	0.036 (0.30)
All-cause mortality, n (%)	390 (4.2)	711 (9.3)
Opioid-related mortality, n (%)	17 (0.18)	23 (0.30)[b]

MME indicates morphine milligram equivalents; VHA, Veterans Health Administration.

[a]Groups are different (P <.0001) for all characteristics except gender and opioid-related mortality (P >.2 for both).

[b]Not significant.

in at least 1 month),[20] concurrent opioid/benzodiazepine use (defined by overlapping prescriptions of at least 1 day),[3,21] and rural status of pharmacy and residence (defined as having a rural designation in Massachusetts). Demographics were gathered from all Chapter 55 data sources; when a conflict was found, it was resolved based on a hierarchy of reliability developed by the Chapter 55 team. The PMP data provided pharmacy location, generic codes of drugs, quantity, and dose.[22] Additional information was obtained from the APCD on homelessness, which is almost certainly an undercount of all persons experiencing homelessness, and comorbidities, including the mental and physical components of the Elixhauser comorbidity index (eAppendix Table).[23] Although the APCD contains health and pharmacy insurance claims data from across the state, it does not include service records from the VHA. Because of concerns that this may lead to differential completeness of data between the study groups, addition of homelessness and comorbidities in the form of an index (which would not have been available to us for VHA-only patients) was analyzed in a separate model.

Data Analysis

Covariates and outcomes were compared between VHA-only and dual care users, using χ^2 and t tests to detect differences. Logistic regression models were constructed for the 3 outcomes, including (1) an unadjusted model and (2) an adjusted model including terms for demographics, high-dose opioid therapy, and concurrent opioid/benzodiazepine use. A third model also included terms for homelessness and Elixhauser comorbidity index. These models were repeated, limiting to veterans who received opioids only. We also examined interaction terms between dual care use and homelessness because of a suspected heterogeneity of effect. Odds ratios (ORs) generated from these logistic regression models, although not entirely intuitive to some readers, are generally similar to more intuitive measures when examining rare outcomes. Analyses were performed using SAS Studio version 3.5 (SAS Corporation; Cary, North Carolina).

RESULTS

Descriptive characteristics of veterans were compared across groups (**Table**). Compared with VHA-only users, more dual care users resided in rural areas (12.6% vs 10.6%), received high-dose opioid therapy (26.3% vs 7.3%), had concurrent prescriptions of opioids and benzodiazepines (34.8% vs 8.2%), had documented opioid use disorder (6.8% vs 1.6%), and were homeless (1.5% vs 0.7%), and they had higher mean physical (3.0 vs 1.3) and mental (0.6 vs 0.2) comorbidity scores (P <.0001 for all). In terms of outcomes, dual care users had more nonfatal overdoses (160 [2.1%] vs 114 [1.2%]) and higher all-cause mortality (711 [9.3%] vs 390 [4.2%]) (P <.0001 for both comparisons).

All 3 study outcomes were more common among dual care users in the unadjusted models (**Figure**). Adjustment for demographics, high-dose opioid therapy, and concurrent opioid/benzodiazepine use attenuated the estimates for nonfatal overdose (OR, 1.29; 95% CI, 0.98-1.71), fatal overdose (OR, 1.32; 95% CI, 0.64-2.70), and all-cause mortality (OR, 1.66; 95% CI, 1.43-1.93). Adjustment for homelessness and comorbidities further attenuated the point estimates (data not shown). There was no significant interaction between dual care use and homelessness. The number of switches between VHA and non-VHA prescriptions was not associated with any outcome. Similar effects were obtained for dual care users with opioid prescriptions only.

DISCUSSION

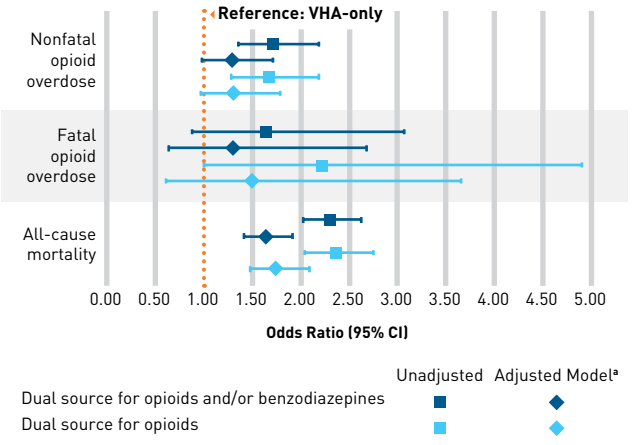
The study is the first collaborative effort of MDPH and VHA to examine VHA and non-VHA care coordination among veterans at risk of opioid overdose. Findings suggest that those receiving opioid and/or benzodiazepine prescriptions from both VHA and non-VHA pharmacies have higher odds of nonfatal opioid overdose

and all-cause mortality compared with veterans receiving controlled substances from the VHA only. Although we found stronger effects of dual care use on nonfatal opioid overdose and all-cause mortality in unadjusted analyses, the multivariate adjustment process reduced this risk, as the variables controlled for may be inherently related to the mechanism of harm. For example, adjusting for rural residence of veterans, shown to be associated with both dual care[24] (the predictor) and opioid overdose[25] (the outcome), might have lessened the risk of nonfatal opioid overdose in multivariate models. Although we found that the risks of opioid-related deaths among dual care users did not reach statistical significance, potentially due to the small number of events, there remains concern that this group is at higher risk of opioid-related mortality. Further, as is evident from the striking differences in baseline characteristics between the 2 groups in regard to receipt of high-dose opioid therapy (26.3% vs 7.3%), concurrent prescriptions for opioids and benzodiazepines (34.8% vs 8.2%), and opioid use disorder (6.8% vs 1.6%), it may be that individuals who seek dual sources of medications are often essentially different than those who do not (and that covariation cannot account for that) and that is the causal direction.

Our finding of association between dual care use and adverse outcomes in Massachusetts veterans is consistent with a previous report suggesting that having multiple payment sources, including VHA, cash, and noncash (Medicare, Medicaid, and private insurance), was associated with increased risky patterns of opioid therapy (overlap with benzodiazepines and/or high-dose opioid therapy) after controlling for age and sex in veterans in the Kentucky PMP.[17] Our study went further, however, by examining outcomes and adjusting for a wider range of potentially confounding variables. Associations of dual pharmacy use with adverse opioid-related outcomes have also been reported in non-VHA populations. Multiple pharmacy use (defined as >2 pharmacies) predicted opioid overdose in Medicaid patients,[12] and obtaining opioid prescriptions from multiple healthcare providers was associated with higher rates of hospital admission related to opioid use.[11]

The proportion of dual care users between VHA and non-VHA pharmacies in our study was approximately 45%. In a recent study, the prevalence of veterans receiving prescription opioids from both VHA and Medicare Part D was reported to be 13.2%.[26] Although fatal opioid overdose was not significantly associated with dual care use in our model, possibly due to limited statistical power, we found that a higher proportion of dual care users had opioid-related mortality compared with VHA-only users (0.30% vs 0.18%). In the context of these findings, our study highlights the importance of PMPs as a potential tool to reduce fractured care, especially regarding opioids, among multiple providers, pharmacies, and healthcare systems both within and across VHA and non-VHA facilities. Through the implementation of its Opioid Safety Initiative in 2013, VHA required contribution of its controlled substance prescribing and dispensing data to state PMPs.[27] In turn, PMPs have been found effective in both reducing adverse events associated with opioid use[28] and reducing prescriptions from multiple providers.[29] Further, the statutory requirements

FIGURE. Association of Nonfatal and Fatal Outcomes With Dual Opioid Use and/or Benzodiazepine Use Compared With VHA-Only Use by Veterans in Massachusetts, 2013-2015



VHA indicates Veterans Health Administration.

[a]Adjusted for age, gender, high-dose opioid therapy, concurrent use of benzodiazepines, number of VHA/non-VHA pharmacy switches by patient, and rurality of the last pharmacy used.

for VHA under the Comprehensive Addiction and Recovery Act (CARA; PL 114-198) enacted in July 2016 mandate a designated Pain Management Team, consisting of healthcare professionals at each facility, responsible for coordinating and overseeing pain management therapy for patients experiencing acute and chronic pain that is not cancer-related. Pursuant to CARA and VHA Directive 1306,[30] in October 2016 it was further required that state PMP databases are queried for VHA patients who are receiving prescriptions for controlled substances on a minimum of an annual basis and that the results of those queries are documented in the VHA medical record.

Strengths and Limitations

An important strength of our study was the use of a rich and unique data set, which captured prescribing of opioids both inside and outside of the VHA. To our knowledge, no other data resource would have supported such an analysis. Further, this study addresses a key issue, dual care use, which is leading to greater likelihood of uncoordinated care among veterans across the United States compared with commercially insured civilians who benefit from PMPs and other strategies known to work in anyone at high risk of overdose. However, like any state, Massachusetts has its own cultural, demographic, and socioeconomic environment, possibly limiting the generalizability of these findings to other states. More importantly, findings from this veteran study cannot be generalized to the general population. Further, we lacked complete information on medical utilization and comorbidities in our VHA-only group, which could confound the associations. Our attempts to include them in the analysis were limited by the recognition that differential completeness in the data between VHA-only patients and dual care use patients may result in bias and that their inclusion in the

models might not lead to accurate results. Another limitation of the Chapter 55 data set was that pharmacy-specific variables such as distance to the pharmacy and number of non-VHA pharmacies could not be included in the model due to lack of patient address, geocoding of pharmacies, and unique pharmacy identifier. Further, in our study, we did not exclude patients with a cancer diagnosis. The findings of this study investigating opioid overdose may not be completely generalizable to the cancer population. A final limitation is that nonfatal overdoses may be underascertained in the study, as not all nonfatal opioid overdoses may involve an encounter with the healthcare system.

CONCLUSIONS

As the VHA is expanding its use of non-VHA care and providers through the Veterans Choice program,[31] compounding the issue of coordination of care across systems, these findings are timely. The present study expands our understanding of opioid-related outcomes. Findings suggest the need not only to continue to share data between VHA and state PMPs but also to take further steps. These steps could include implementing prescription drug disposal, safe opioid prescribing education, aggressive dispensing of naloxone to veterans and their families, including specific alerts in PMPs regarding patients with previous histories of dual care use, and providing these dual care users more resources and closer care coordination, especially with regard to opioids. ■

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eAppendix Table. Definition of Variables Used in the Study

Variables	Definition	Codes (if applicable)
Opioid fill	Filled prescription for all opioids, including tramadol and buprenorphine, between October 1, 2013, and December 31, 2015	Generic Cross Reference (GCR) Codes for all opioids: 930981, 930133, 930052, 930049, 930041, 929758, 929645, 929451, 929414, 929410, 929182, 929026, 928771, 928553, 928363, 928354, 928318, 927685, 927600, 927029, 926797, 926762, 926665, 926663, 926662, 926660, 926658, 926654, 926652, 926650, 926649, 926647, 926646, 926525, 926524, 926119, 926108, 926105, 926104, 926103, 925351, 924365, 923958, 923776, 923770, 923767, 923563, 923420, 923042, 921976, 921975, 921974, 629767, 596370, 492885, 492829, 492826, 487682, 487595, 464966, 464956, 464832, 453380, 453360, 432417, 432185, 432180, 423500, 423470, 382310, 371260, 368265, 368240, 337990, 302774, 292100, 291500, 291490, 291485, 291478, 291473, 291455, 265100, 226300, 226295, 208775, 180129, 130984, 130970, 130964, 130959, 108155, 095670, 092577, 004050, 004046, 923288, 931161, 931282
High-dose opioid therapy	Average daily morphine milligram equivalents higher than 50	
Concurrent use of opioid/benzodiazepine	Benzodiazepine prescriptions concurrently filled with any opioid during any month between October 1, 2013, and December 31, 2015	GCR codes for benzodiazepines: 119270, 119185, 213000, 927904, 431685, 214420, 930123, 236575, 375025, 594000, 923630, 176990, 347844, 929700, 624620, 127780, 931138, 930120, 924008, 498000
Rural residence	Rural status of the town of patients' latest residence	
Rural status of the pharmacy	Rural status of the town of last pharmacy where patient filled the opioid prescription	
Homelessness	A binary variable based on ever mention of homelessness *ICD-9-CM* or *ICD-10* codes in the All Payers Claims Database (APCD) (defined by MDPH)	*ICD-9*: V600 *ICD-10*: Z590
Elixhauser physical comorbidities	Count of Elixhauser physical comorbidities ever diagnosed between January 1, 2011, and December 31, 2015; based on diagnosis codes in APCD; range 0-27	HIV, liver disease, chronic pulmonary disease, CHF, arrhythmia, valvular heart, pulmonary circulatory, peripheral vascular, hypertension (uncomplicated and complicated), paralysis, other neurologic, diabetes (uncomplicated and complicated), acid peptic disease, renal failure, non-metastatic cancer, metastatic cancer, rheumatoid arthritis/autoimmune diseases, coagulopathy, obesity, weight loss, anemia (blood loss and deficiency), fluid and electrolyte imbalance
Elixhauser mental comorbidities	Count of Elixhauser physical comorbidities ever diagnosed between January 1, 2011, and December 31, 2015; based on diagnosis codes in APCD; range 0-4	Alcohol dependence, substance use, depression, psychosis
Opioid use disorder	A binary variable based on any mention of opioid use *ICD-9-CM* or *ICD-10* codes in APCD (defined by MDPH)	*ICD-9-CM*: 30400, 30401, 30402, 30403, 30470, 30471, 30472, 30473, 30550, 30551, 30552, 30553 *ICD-10*: F1120, F1121, F1110, F11120, F11121, F11122, F11129, F1114, F11150, F11151, F11159, F11181,

		F11182, F11188, F1119, F11220, F11221, F11222, F11229, F1123, F1124, F11250, F11251, F11259, F11281, F11282, F11288, F1129, F1190, F11920, F11921, F11922, F11929, F11913, F11914, F11950, F11951, F11959, F11981, F11982, F11989, F1199
Nonfatal opioid overdose	A binary variable based on ambulance encounters, emergency department visits, outpatient observation, or inpatient hospital discharge.	ICD-9-CM: 965.00-965.02, 965.09, E85.00-E85.02
Fatal opioid overdose	A binary variable based on identification of diagnoses codes for mortality and opioid-related poisoning	ICD-10-CM: X40-X49, Y10-Y19 T40.0, T40.1, T40.2, T40.3, T40.4, and T40.6