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Dual Receipt of Prescription Opioids From the Department of Veterans Affairs and Medicare Part D and Prescription Opioid Overdose Death Among Veterans

A Nested Case–Control Study

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Background: More than half of enrollees in the U.S. Department of Veterans Affairs (VA) are also covered by Medicare and can choose to receive their prescriptions from VA or from Medicare-participating providers. Such dual-system care may lead to unsafe opioid use if providers in these 2 systems do not coordinate care or if prescription use is not tracked between systems.

Objective: To evaluate the association between dual-system opioid prescribing and death from prescription opioid overdose.

Design: Nested case–control study.

Setting: VA and Medicare Part D.

Participants: Case and control patients were identified from all veterans enrolled in both VA and Part D who filled at least 1 opioid prescription from either system. The 215 case patients who died of a prescription opioid overdose in 2012 or 2013 were matched (up to 1:4) with 833 living control patients on the basis of date of death (that is, index date), using age, sex, race/ethnicity, disability, enrollment in Medicaid or low-income subsidies, managed care enrollment, region and rurality of residence, and a medication-based measure of comorbid conditions.

Measurements: The exposure was the source of opioid prescriptions within 6 months of the index date, categorized as VA only, Part D only, or VA and Part D (that is, dual use). The outcome was unintentional or undetermined-intent death from prescription opioid overdose, identified from the National Death Index. The association between this outcome and source of opioid prescriptions was estimated using conditional logistic regression with adjustment for age, marital status, prescription drug monitoring programs, and use of other medications.

Results: Among case patients, the mean age was 57.3 years (SD, 9.1), 194 (90%) were male, and 181 (84%) were non-Hispanic white. Overall, 60 case patients (28%) and 117 control patients (14%) received dual opioid prescriptions. Dual users had significantly higher odds of death from prescription opioid overdose than those who received opioids from VA only (odds ratio [OR], 3.53 [95% CI, 2.17 to 5.75]; $P < 0.001$) or Part D only (OR, 1.83 [CI, 1.20 to 2.77]; $P = 0.005$).

Limitation: Data are from 2012 to 2013 and cannot capture prescriptions obtained outside the VA or Medicare Part D systems.

Conclusion: Among veterans enrolled in VA and Part D, dual use of opioid prescriptions was independently associated with death from prescription opioid overdose. This risk factor for fatal overdose among veterans underscores the importance of care coordination across health care systems to improve opioid prescribing safety.

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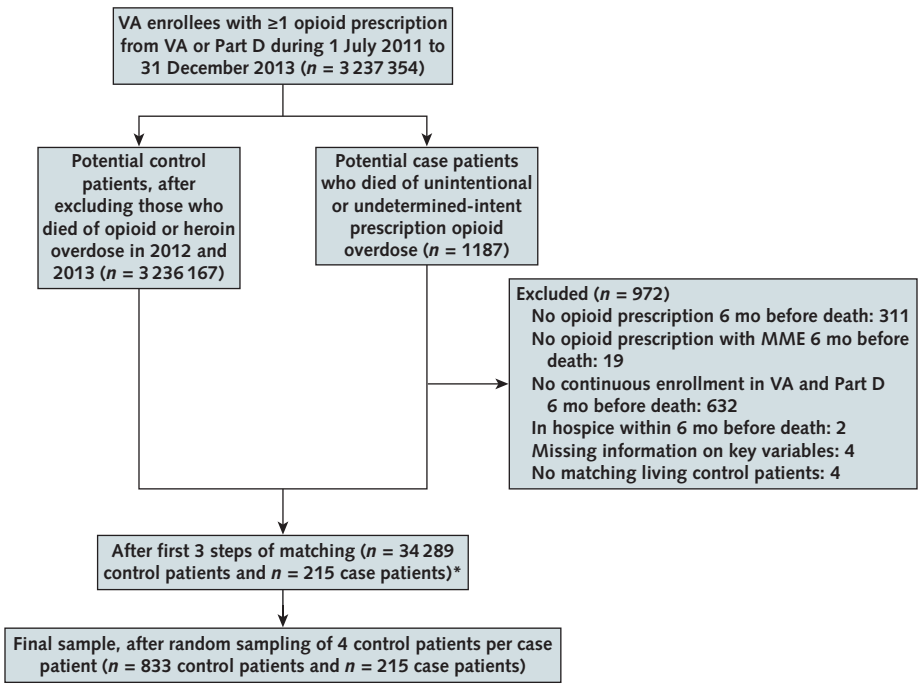
Amid the ongoing opioid crisis in the United States, the health care system of the U.S. Department of Veterans Affairs (VA) has adopted several strategies to reduce opioid overprescribing and related adverse health outcomes (1, 2). Although these efforts by the largest integrated health care system in the country include robust monitoring of opioid prescriptions dispensed within VA, less attention has been directed toward opioids dispensed to VA enrollees through non-VA providers and non-VA insurance. Yet, approximately 80% of VA enrollees have other types of public or private health insurance coverage. More than half (51%) have Medicare, and of these, nearly a third are also enrolled in the Medicare Part D prescription drug benefit (3). The number of veterans using alternative sources of medical and prescription benefits in addition to receiving care at VA facilities is likely to increase given ongoing reforms to bolster access to non-VA care through VA's community care programs (4, 5).

Use of both VA and non-VA providers may increase the complexity of medication management by limiting providers' ability to monitor and coordinate services because of limited information sharing across health systems (6–13). Furthermore, use of multiple health systems could undermine the effectiveness of VA's internal efforts to discourage opioid overuse and reduce opioid-related harms (14, 15). Evidence from prior studies indicates that receipt of care from unconnected health systems is associated with excess use and costs

See also:

Editorial comment 497

Figure 1. Selection criteria for case and control patients.



MME = morphine milligram equivalent; VA = U.S. Department of Veterans Affairs.
* Matching proceeded in 4 steps: The first 3 allowed replacement of control patients, and the final step was without replacement. Therefore, unique control patients could be possible matches for ≥1 case patient before the last step. First, we matched control patients to case patients on the 5 time-invariant variables (birthdate ±5 y, sex, race/ethnicity, region of residence, and rurality of residence), and assigned the date of death from each case patient as the index date for matched control patients (n = 1 522 446 unique control patients matched to n = 219 case patients). Second, we applied the same exclusion criteria to control patients as described for case patients (n = 271 805 unique control patients matched to n = 219 case patients). Third, we matched case and control patients on the 4 time-variant variables (disability as the reason for Medicare enrollment [year of death], enrollment in Medicaid and Part D low-income subsidy [prior 6 mo], Medicare managed care enrollment [prior 6 mo], and medication-based comorbidity index [Rx-Risk, prior 6 mo]; n = 34 289 unique control patients were matched to n = 215 case patients, including 10 case patients with <4 control patients). Finally, we randomly sampled up to 4 control patients per case patient without replacement (n = 833), where 205 case patients had 4 control patients each, 7 had 1 control patient, and 3 had 2 control patients. The final number of case patients was 215 after exclusion of 4 who lacked any matches on the 4 time-varying variables.

(9, 16–18) and increased risk for potentially unsafe prescribing of opioids and other medications (11, 12, 19, 20). Among veterans dually enrolled in VA and Part D, receiving opioids from both systems (that is, dual use) is associated with significantly increased risk for high-dose opioid exposure (12) and overlapping opioid and benzodiazepine prescriptions (20), both of which are strongly associated with increased risk for overdose death (21–23).

Although the association between dual use and unsafe medication use is now well established, no prior study to our knowledge has evaluated the association between dual use and adverse health outcomes of unsafe prescribing, such as overdose death. Veterans are at increased risk for opioid use disorders and have fatal accidental overdoses at nearly twice the rate seen in U.S. adults (24). We aimed to assess the association between dual receipt of opioid prescriptions from VA and Part D and death from prescription opioid overdose among veterans enrolled in both systems. We hypothesized that dual users would be more likely to die of prescription opioid overdose than those receiving opioids through 1 system only.

METHODS

We conducted a nested case–control study in a previously defined cohort of more than 3.2 million veterans who filled at least 1 opioid prescription from either VA or Part D between 1 July 2011 and 31 December 2013. We chose a case–control approach because death from prescription opioids is a relatively infrequent health outcome at the population level. The nested case–control design ensures that case and control patients are derived from the same source population. The VA Pittsburgh Healthcare System Institutional Review Board approved this study.

Data Sources

We linked national patient-level data from the VA and Centers for Medicare & Medicaid Services in calendar years 2011 to 2013. Data from the Centers for Medicare & Medicaid Services were unredacted and included substance abuse claims. Veteran demographic characteristics came from the VA Corporate Data Warehouse and Medicare beneficiary summary files. We obtained information on outpatient prescription medications from VA Pharmacy Benefits Manage-

ment Services and Medicare Part D. We determined cause of death using the National Death Index, a comprehensive epidemiologic resource of death certificates from all state vital statistics offices (25). National Death Index data for all veterans are stored in the Joint Department of Defense–VA Suicide Data Repository, and data from 2013 were the most recent available during the study (26). We obtained ZIP code of patient

Table 1. Characteristics of Case Patients Who Died of Prescription Opioid Overdose and Matched Control Patients

Characteristic	Case Patients (*N* = 215), *n* (%)	Control Patients (*N* = 833), *n* (%)	*P* Value*
Matching variables			
Mean age at index date (SD), *y*	57.3 (9.1)	58.3 (8.6)	0.001
Age			
18–39 y	11 (5.1)	21 (2.5)	0.014
40–64 y	170 (79.1)	635 (76.2)	0.014
≥65 y	34 (15.8)	177 (21.2)	0.014
Male	194 (90.2)	769 (92.3)	NA
Race/ethnicity			
Non-Hispanic white	181 (84.2)	703 (84.4)	NA
Non-Hispanic black	23 (10.7)	86 (10.3)	NA
Hispanic and non-Hispanic other†	11 (5.1)	44 (5.3)	NA
Region of residence			
Northeast	25 (11.6)	94 (11.3)	NA
Midwest	47 (21.9)	186 (22.3)	NA
South	83 (38.6)	326 (39.1)	NA
West	60 (27.9)	227 (27.3)	NA
Rurality of residence			
Large metropolitan	97 (45.1)	374 (44.9)	NA
Small metropolitan	77 (35.8)	300 (36.0)	NA
Micropolitan	23 (10.7)	89 (10.7)	NA
Noncore rural	18 (8.4)	70 (8.4)	NA
Disability 6 mo before index date‡	196 (91.2)	757 (90.9)	NA
Medicaid and low-income subsidy 6 mo before index date			
Had Medicaid	109 (50.7)	428 (51.4)	NA
Had LIS but not Medicaid	31 (14.4)	115 (13.8)	NA
Did not have Medicaid or LIS	75 (34.9)	290 (34.8)	NA
Any Medicare managed care enrollment 6 mo before index date	60 (27.9)	234 (28.1)	NA
Mean RxRisk-V score 6 mo before index date (SD)	7.1 (2.8)	7.0 (2.7)	0.110
Other covariates			
Marital status			
Married	45 (20.9)	286 (34.3)	<0.001
Divorced, separated, or widowed	124 (57.7)	383 (46.0)	<0.001
Never married	35 (16.3)	111 (13.3)	<0.001
Unknown or missing	11 (5.1)	53 (6.4)	<0.001
Medication use 6 mo before index date			
Antidepressants	136 (63.3)	442 (53.1)	0.008
Antipsychotics	64 (29.8)	138 (16.6)	<0.001
Gabapentin or pregabalin	106 (49.3)	238 (28.6)	<0.001
Benzodiazepines	112 (52.1)	238 (28.6)	0.004
Muscle relaxants	93 (43.3)	267 (32.1)	<0.001
Sleep aids	42 (19.5)	129 (15.5)	0.145
Mean nonopioid drugs used (SD), *n*	10.6 (5.1)	9.8 (4.9)	<0.001
Operational PDMP before index date	201 (93.5)	763 (91.6)	0.40
Fee-for-service–only subsample§			
Alcohol and substance use disorders 6 mo before index date	80 (51.6)	121 (20.2)	<0.001
Cancer	<11	24 (4.0)	0.47
RIOSORD comorbid conditions and health service use measures			
Hepatitis or cirrhosis	37 (23.9)	64 (10.7)	<0.001
Bipolar disorder or schizophrenia	49 (31.6)	97 (16.2)	<0.001
Chronic pulmonary disease	63 (40.6)	157 (26.2)	<0.001
End-stage renal disease	18 (11.6)	36 (6.0)	0.013
Active traumatic injury	40 (25.8)	111 (18.5)	0.035
Sleep apnea	<11	70 (11.7)	0.025
Any hospitalization 6 mo before index date	107 (69.0)	266 (44.4)	<0.001
Any ED visit 6 mo before index date	69 (44.5)	142 (23.7)	<0.001

ED = emergency department; LIS = low-income subsidy; NA = not applicable; PDMP = prescription drug monitoring program; RIOSORD = Risk Index for Overdose or Serious Opioid-Induced Respiratory Depression.
* NA for categorical variables because of exact matching.
† Grouped only for table presentation to avoid displaying cell sizes <11, per the data use agreement policy of the Centers for Medicare & Medicaid Services. "Hispanic" and "non-Hispanic other" were treated as 2 separate categories in matching.
‡ Disability as the original reason for Medicare eligibility.
§ 155 case patients and 599 control patients.

Table 2. Association Between Source of Opioid Prescription and Unintentional Death From Prescription Opioid Overdose in Veterans Enrolled in Both VA and Medicare Part D

Source of Opioid Prescriptions	Case Patients (*N* = 215), *n* (%)	Control Patients (*N* = 833), *n* (%)	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)*	*P* Value
VA only (*n* = 321)	42 (19.5)	279 (33.5)	1.00 (reference)		1.00 (reference)	
Part D only (*n* = 550)	113 (52.6)	437 (52.5)	1.73 (1.17–2.57)	0.006	1.93 (1.26–2.95)	0.002
Dual use (*n* = 177)	60 (27.9)	117 (14.0)	3.36 (2.13–5.29)	<0.001	3.53 (2.17–5.75)	<0.001
Dual use vs. Part D only	NA	NA	1.94 (1.31–2.86)	<0.001	1.83 (1.20–2.77)	0.005

NA = not applicable; OR = odds ratio; VA = U.S. Department of Veterans Affairs.
* Adjusted for patient demographic characteristics, including age, marital status, prescription drug monitoring program operational status, and medication use ≤180 d before the index date (antidepressants, antipsychotics, and total number of nonopioid drugs).

residence from Public Safety Strategies Group data on VA enrollee geocodes, and census region and urban influence code from the Area Health Resources File.

Identification of Case and Control Patients

We defined case patients as veterans who died of a prescription opioid overdose that was unintentional or of indeterminate intent between 1 January 2012 and 31 December 2013, determined by the presence of underlying cause-of-death code X42, X44, Y12, or Y14 from the International Classification of Diseases, 10th Revision (ICD-10), in combination with code T40.2, T40.3, or T40.4 (**Appendix**, available at Annals.org) (27). We excluded suicides and overdose deaths attributed to heroin to focus exclusively on prescription opioids, which are in theory more directly linked to dual prescribing. Case patients were also required in the 6 months before death to be continuously enrolled in both VA and Part D and to fill at least 1 opioid prescription. We excluded case patients whose only opioid either was a formulation for which reliable morphine milligram equivalents (MME) could not be computed (for example, oral liquid) or was intended solely for treatment of substance use disorder (that is, buprenorphine–naloxone or liquid methadone). We also excluded case patients who received hospice services or had missing information on key variables. We defined index date as the date of death.

We matched up to 4 living control patients with each case patient on the basis of 9 variables. We initially matched patients on the 5 time-invariant variables (birthdate ±5 years, sex, race/ethnicity, region of residence, and rurality of residence). We then assigned the date of death from each case patient as the index date for matched control patients and proceeded to match on 4 time-variant variables (disability as the reason for Medicare enrollment in index year; enrollment in Medicaid and Part D low-income subsidy in prior 6 months; Medicare managed care enrollment in prior 6 months; and a medication-based comorbidity index, the adapted RxRisk-V [28], in prior 6 months). We captured race/ethnicity from VA data supplemented by the Research Triangle Institute race/ethnicity indicator from Medicare (when missing from VA data). We used all medications prescribed through VA and Part D to calculate the RxRisk-V score. This validated measure of comorbidity classifies prescribed medications into 45 disease-related categories and predicts all-cause mortality with good discrimination (28). Because medical comorbid conditions are systematically undercoded in VA compared with Medicare, we chose to adjust for comorbidity using RxRisk-V; this measure is less susceptible to measurement discrepancies across health systems than the Elixhauser index, which ascertains 30 comorbidity indicators from diagnosis codes (28–31).

We applied all selection criteria equally to case and control patients through a matching process comprising 4 steps, of which the first 3 allowed replacement of control patients and the last did not. First, we matched patients on the time-invariant variables and assigned the date of death from each case patient as the index date for matched control patients. Second, we filtered control patients according to the same inclusion criteria described earlier for case patients, although control patients had to be alive on the case patient's index date. This step ensured that control patients received at least 1 opioid prescription within 6 months before the index date to define the source of these prescriptions. Third, we matched case and control patients on the time-variant covariates. Finally, we randomly sampled up to 4 control patients per case patient without replacement (**Figure 1**).

Definition of the Exposure of Interest

For all case and control patients, we identified sources of opioid prescriptions (VA only, Part D only, or both VA and Part D) dispensed within 6 months before the index date. Part D–only and VA-only users were veterans who obtained all opioid prescriptions through Part D or VA, respectively. Dual users obtained at least 1 opioid prescription from each source.

Definition of Covariates

We used data from the VA and Centers for Medicare & Medicaid Services to identify potential confounders of the association between our exposure of interest and death from prescription opioid overdose. These included marital status (32) and presence of an operational prescription drug monitoring program (PDMP) before the index date in the veteran's state of residence (33). We accounted for differences in health status by creating indicators for the total number of nonopioid medications used within 180 days before the index date and for use of antidepressants and antipsychotics (as proxies for psychiatric conditions) (12). We accessed dates of PDMP operation from the data portal of the Prescription Drug Abuse Policy System (34). Because case and control patients were balanced

on all matching variables except age, we also included a categorical age variable as a covariate. We described opioid dose, use of benzodiazepines, and use of other central nervous system depressants but excluded these from the main analysis because prior studies indicate that these variables lie in the causal pathway between exposure and outcome and are thus unsuitable for model adjustment (12, 20, 35).

In a sensitivity analysis restricted to fee-for-service enrollees (because diagnosis codes are incomplete for enrollees of Medicare managed care plans), we also used ICD, Ninth Revision, codes from claims to adjust for alcohol and drug use disorders and comorbid conditions from the Risk Index for Overdose or Serious Opioid-Induced Respiratory Depression (RIOSORD) (36, 37). The RIOSORD measurements included hepatitis or cirrhosis, bipolar disorder or schizophrenia, chronic pulmonary disease, end-stage renal disease, traumatic injury, sleep apnea, emergency department visits, and hospitalizations. We then adjusted for the presence of these characteristics within 12 months before the index date because they are recognized as risk factors for nonfatal and fatal overdose (38–40). This sensitivity analysis also adjusted for cancer diagnosis.

Measures of Opioid Use

We compared patterns of prescription opioid use in case and control patients across the 3 categories of the exposure variable: dual use, VA-only use, and Part D–only use. During the 180 days before the index date, we measured the number of days with prescription opioid supply, the number of days with more than 120 MME, cumulative MME dose, and average daily MME for the days patients had opioid supply. We used previously described methods (12, 20) to estimate daily opioid doses. In addition, we estimated the extent of dual use by calculating the proportion of opioid days' supply obtained from VA among dual users. We also identified the types of opioids prescribed, by case versus control patients and by source of opioid prescriptions.

Statistical Analysis

We calculated descriptive characteristics of case and control patients and used univariate conditional logistic regression (SAS PROC LOGISTIC with STRATA option) to compare case and control patients. We used multivariable conditional logistic regression to account for matching in assessing the association between the exposure of interest and death from prescription opioid overdose. We quantified the magnitude and precision of the association using odds ratios (ORs) and corresponding 95% CIs in unadjusted models and models adjusting for the previously described covariates. We used the Wilcoxon rank-sum test to assess between-group differences in the medians and interquartile ranges (IQRs) for the opioid use measures.

We did several sensitivity analyses. First, we repeated the analyses using case and control patients who were further matched on VA facility to account for potential differences in practices that affect opioid prescribing, patient care, and use of non-VA providers. Second, we repeated the analysis with additional statistical adjustment for differences between case and control patients in overlapping use of opioids and benzodiazepines, high opioid dosage, and use of gabapentin or pregabalin. Third, among fee-for-service enrollees, we adjusted for additional comorbid conditions, including measures from the RIOSORD index, alcohol and drug use disorders, and cancer (36–40). Fourth, we defined the exposure variable as dual use of any prescription medication, not only opioids. Finally, we assessed

Table 3. Estimates for Covariates Included in the Main Model for the Association Between Source of Opioid Prescription and Unintentional or Undetermined-Intent Death From Prescription Opioid Overdose

Characteristic	Adjusted OR (95% CI)*	*P* Value
Source of opioid prescriptions		
VA only	1.00 (reference)	
Part D only	1.93 (1.26–2.95)	0.002
Dual use	3.53 (2.17–5.75)	<0.001
Dual use vs. Part D only	1.83 (1.20–2.77)	0.005
Age, effect per 1-y change	0.92 (0.86–0.99)	0.017
Marital status		
Married	1.00 (reference)	
Divorced, separated, or widowed	2.24 (1.28–3.93)	<0.001
Never married	1.55 (0.71–3.36)	0.005
Unknown or missing	1.55 (0.71–3.36)	0.27
Medication use 6 mo before index date		
Antidepressants	1.40 (0.97–2.02)	0.069
Antipsychotics	2.08 (1.40–3.10)	<0.001
Mean number of nonopioid drugs, effect per 1-unit change	1.06 (1.01–1.12)	0.029
Operational PDMP before index date	1.40 (0.71–2.78)	0.33

OR = odds ratio; PDMP = prescription drug monitoring program; VA = U.S. Department of Veterans Affairs.
* Adjusted for patient demographic characteristics, including age, marital status, PDMP operational status, and medication use ≤180 d before the index date (antidepressants, antipsychotics, and total number of nonopioid drugs).

Table 4. Patterns of Opioid Use Among Case and Control Patients Dually Enrolled in VA and Medicare Part D, by Source of Opioid Prescriptions

Source of Opioid Prescriptions 180 Days Before Death	Median Days With Opioid Supply (IQR)			Median Days With MME >120 (IQR)			Median Total MME Over 6 Months (IQR)			Median Average Daily MME (IQR)*		
	Case Patients	Control Patients	*P* Value	Case Patients	Control Patients	*P* Value	Case Patients	Control Patients	*P* Value	Case Patients	Control Patients	*P* Value
Total†	165 (93–179)	132 (33–175)		22 (0–151)	0 (0–8)		14 341 (2821–37 620)	3946 (900–12 795)		98 (40–227)	40 (23–84)	
VA only‡	169 (73–177)	143 (62–173)	0.051	6 (0–125)	0 (0–1)	<0.001	9073 (1425–26 595)	3833 (1040–10 260)	0.012	74 (25–150)	33 (19–62)	0.006
Part D only§	154 (60–177)	91 (17–173)		19 (0–151)	0 (0–8)		12 000 (2075–39 240)	2915 (413–12 480)		105 (40–254)	42 (25–100)	
Dual use‖	175 (135–180)	173 (131–180)	0.65	51 (2–156)	0 (0–39)	<0.001	16 828 (6863–40 989)	6980 (3440–20 385)	0.004	104 (54–230)	53 (30–113)	<0.001

IQR = interquartile range; MME = morphine milligram equivalents; VA = U.S. Department of Veterans Affairs.
* We calculated the average daily MME dose on days with opioid supply and then obtained median values of these average daily doses.
† All *P* values < 0.001. Included 215 case and 833 control patients (*n* = 1048).
‡ Included 42 case and 279 control patients (*n* = 321).
§ All *P* values < 0.001. Included 113 case and 437 control patients (*n* = 550).
‖ Included 60 case and 117 control patients (*n* = 177).

the strength of potential unobserved confounding that would be required to nullify the observed association between dual use of opioids and overdose death according to specified plausible values of the prevalence of an unmeasured confounder among exposed patients (dual users) and unexposed patients (VA-only users), and the relative risks between the confounder and overdose death (41, 42). We used the EPISENSRRI module in Stata, version 14 (StataCorp), for the unobserved confounder assessment. All other analyses were done using SAS Enterprise Guide, version 7.1 (SAS Institute).

Role of the Funding Source

The funders had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation of the manuscript.

RESULTS

We identified 1187 persons who died of a prescription opioid overdose, of whom 225 (19.0%) filled at least 1 opioid prescription for which MME could be reliably measured and were continuously enrolled in both VA and Part D in the 6 months before death (Figure 1). From these potentially eligible case patients, we excluded 10 because of receipt of hospice services (*n* = 2), missing information on matching variables (*n* = 4), or absence of any matching living control patients (*n* = 4). For 10 case patients (4.7%) who had fewer than 4 eligible matches, we matched and analyzed any available control patients. The final analytic sample comprised 215 case and 833 control patients; 205 case patients had 4 matched control patients, 3 had 2 control patients, and 7 had 1 control patient.

Table 5. Extent of Dual Use as Defined by Percentage of Days' Supply of Opioids Obtained From VA

Days of Opioids Supplied From VA Among Dual Users	Case Patients (*n* = 60)	Control Patients (*n* = 117)
Mean (SD), %	63.3 (25.0)	58.6 (31.6)
Median (IQR), %	56.0 (49.4–85.9)	54.7 (37.0–90.8)

IQR = interquartile range; VA = U.S. Department of Veterans Affairs.

Case patients had a mean age of 57.3 years (SD, 9.1), 90.2% were male, 84.2% were non-Hispanic white, 91.2% were disabled, and 27.9% were enrolled in Medicare managed care (Table 1). Case patients were slightly younger than control patients (mean age, 57.3 vs. 58.3 years; $P = 0.001$), but the remaining matched variables did not differ significantly between groups. For variables not used in matching, case patients differed from control patients by marital status ($P < 0.001$) and were significantly more likely to have received antidepressants (63.3% vs. 53.1%; $P = 0.008$), antipsychotics (29.8% vs. 16.6%; $P < 0.001$), gabapentin or pregabalin (49.3% vs. 28.6%; $P < 0.001$), or benzodiazepines (52.1% vs. 28.6%; $P = 0.004$) in the 6 months before their index date.

Overall, 60 case patients (27.9%) and 117 control patients (14.0%) received opioid prescriptions from both VA and Medicare Part D within 6 months of the index date (Table 2). Nearly 53% of case and control patients obtained opioids from Part D only. Compared with veterans who received opioids from VA only, those who received opioids from Part D only or from both VA and Part D (dual users) had significantly higher odds of death from prescription opioid overdose (OR, 1.93 [95% CI, 1.26 to 2.95] and OR, 3.53 [CI, 2.17 to 5.75], respectively). The adjusted odds of death were also significantly higher for dual users than Part D–only users (OR, 1.83 [CI, 1.20 to 2.77]); Table 3 gives full model results.

Across all 4 measures of opioid use examined, case patients had greater levels of opioid exposure than control patients (Table 4). Among case patients, dual users and VA-only users had similar numbers of days with opioid supply (median, 175 days [IQR, 135 to 180 days] vs. 169 days [IQR, 73 to 177 days]), but dual users had more days with MME higher than 120 (median, 51 days [IQR, 2 to 156 days] vs. 6 days [IQR, 0 to 125 days]). Dual users also had a higher cumulative opioid dose over 180 days (median, 16 828 MME [IQR, 6863 to 40 989 MME] vs. 9073 MME [IQR, 1425 to 26 595 MME]) and a higher average daily opioid dose (median, 104 MME [IQR, 54 to 230 MME] vs. 74 MME [IQR, 25 to 150 MME]). The extent of dual use, measured as the proportion of days' supply obtained from VA, was

similar between case and control patients (Table 5). Table 6 shows the frequencies of opioids prescribed by type.

The main results remained essentially unchanged in sensitivity analyses that varied model specifications, except that the comparison of dual use with Part D–only use was no longer statistically significant in a subset of these analyses (Appendix Tables 1 to 4, available at Annals.org). In the sensitivity analysis limited to Medicare fee-for-service enrollees using claims-based risk adjustment, the odds of overdose death were 4 times higher in dual users than VA-only users (OR, 4.04 [CI, 2.11 to 7.74]) (Appendix Table 3). We further assessed the potential for unobserved confounding to affect our main results. For the finding comparing dual use with VA-only use, an unobserved confounder would need to have both a relative risk ratio of at least 9.8 with opioid overdose death and an OR of 15.7 or greater for an association with dual use to nullify the observed OR of 3.53 (Figure 2).

DISCUSSION

This national case–control study of all veterans dually enrolled in VA and Medicare Part D extends prior research on dual-system opioid prescribing by examining overdose death—the ultimate outcome targeted by many policies of VA and other national organizations. We found that receipt of opioid prescriptions from both VA and Part D was associated with 2 to 3 times greater odds of overdose death than receipt of opioids from VA or Part D alone.

As options expand for VA enrollees to simultaneously receive care outside VA, it is important to recognize and respond to the threat that health care fragmentation poses to quality of care, patient safety, and health outcomes. This study highlights the extent of potential consequences of dual-system use, which go beyond economic costs and poor medication safety and include increased risk for death from prescription opioid overdose. Therefore, coordination of VA and non-VA pharmacy care should be a policy priority to more effectively promote safe prescribing of opioids and other medications for the sizeable population of veterans who receive medication both inside and outside VA.

Although the strong associations found in our observational study cannot establish causality, plausible mechanisms exist by which dual use could lead to higher risk for overdose. Dual use is known to increase the likelihood of uncoordinated and poorly managed care, which can increase risk for accidental death from prescription opioid overdose due to duplicative prescriptions. Like prior research (12, 20), our study found higher-intensity opioid use and greater rates of opioid dosages higher than 120 MME among dual users than VA-only or Part D–only users. However, controlling for opioid dose, alcohol and substance use disorders, and RIOSORD measures minimally attenuated the observed effect. Although these covariates could partially explain the observed effect, dual use and prescription opioid overdose death still have a substantial relationship even after adjustment for covariates. Our sensitivity analysis indicated that confounding would have to be implausibly large to annul the observed association. Regardless of causality, however, these results make clear that dual use is an important marker of elevated risk for fatal overdose.

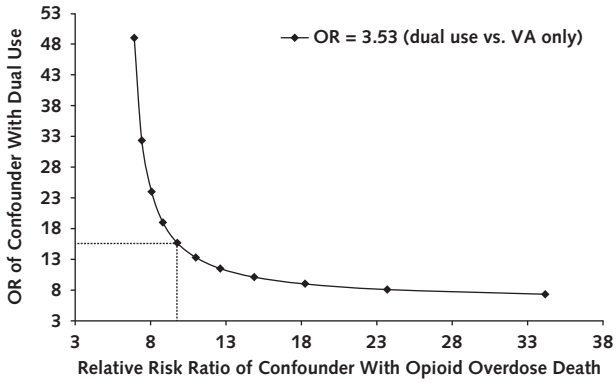
Prescription drug monitoring programs, now operational in every state, can help address multisystem dispensing of prescription medications. To date, PDMPs are the only tool that collects comprehensive data on the dispensing of controlled medications across all payer sources, including most VA facilities as of 2016. When queried and interpreted appropriately, which is not guaranteed, PDMP data may be beneficial in efforts to coordinate VA and non-VA opioid prescribing for veterans who are dual users. The VA has promoted PDMP use as part of its Opioid Safety Initiative, and new national requirements suggest that PDMP uptake will improve. For example, a VA directive now mandates that health care providers query the database before starting opioid therapy, and the VA Prescription Data Accountability Act, signed into law in 2017, requires VA facilities to report pharmacy data to their respective state PDMPs to the extent necessary to prevent misuse and diversion (43). The VA is also working to integrate PDMP results into its electronic medical record, although this effort is still far from implementation. Of note, although PDMPs can help identify dual users and may reduce the prevalence of dual use,

Table 6. Type of Opioid Used, by Case vs. Control Patients and by Source of Opioids

Opioids	Case Patients (*N* = 215), *n* (%)	Control Patients (*N* = 833), *n* (%)	VA Only (*N* = 321), *n* (%)	Part D Only (*N* = 550), *n* (%)	Dual Use (*N* = 177), *n* (%)
Hydrocodone	114 (53.0)	467 (56.1)	156 (88.1)	299 (54.4)	126 (39.3)
Tramadol	49 (22.8)	183 (22.0)	87 (49.2)	83 (15.1)	62 (19.3)
Oxycodone	121 (56.3)	292 (35.1)	79 (44.6)	238 (43.3)	96 (29.9)
Codeine	*	59 (7.1)	24 (13.6)	34 (6.2)	*
Morphine	54 (25.1)	104 (12.5)	61 (34.5)	64 (11.6)	33 (10.3)
Fentanyl	30 (14.0)	30 (3.6)	11 (6.2)	34 (6.2)	15 (4.7)
Methadone	31 (14.4)	55 (6.6)	21 (11.9)	38 (6.9)	27 (8.4)
Hydromorphone	15 (7.0)	23 (2.8)	*	28 (5.1)	*
Other†	14 (6.5)	17 (2.0)	*	26 (4.7)	*

VA = U.S. Department of Veterans Affairs.
* Numbers <11 are suppressed.
† Includes buprenorphine, meperidine, oxymorphone, and tapentadol.

Figure 2. Sensitivity analysis to identify the level of confounding necessary to nullify the association between receipt of prescription opioids from VA and Medicare Part D and unintentional death from prescription opioid overdose among veterans.



The plot was drawn by assuming a fixed prevalence (50%) of the unmeasured confounder among exposed persons (dual users) and a plausible prevalence among unexposed persons (VA-only users) ranging from 2% to 12%. The relative risk ratio of a confounder with opioid overdose death needed to nullify the observed adjusted OR ranged from 6.5 to 34.1 (*x*-axis), and the corresponding OR of the confounder with dual use ranged from 49.0 to 7.3 (*y*-axis). The area above and to the right of the curved plotted line represents values of the levels of confounding necessary to produce the observed adjusted OR (3.53) in our study. The area below and to the left of the line represents levels of confounding that would not be sufficient on its own, after adjustment for observed variables, to produce the observed OR. For example, the dashed lines indicate that for a confounder with a prevalence of 50% among exposed persons and 6% among unexposed persons, a relative risk ratio ≥9.8 with opioid overdose death (*x*-axis), and an OR ≥15.7 with dual VA and Part D use (*y*-axis) would be needed to nullify our observed adjusted OR. OR = odds ratio; VA = U.S. Department of Veterans Affairs.

whether they will affect the safe use of opioids in VA and ultimately decrease unintentional deaths from prescription overdose is unknown. Additional efforts are in place to address risk for overdose (2, 44), such as implementation of the Stratification Tool for Opioid Risk Mitigation, which prioritizes individuals for review according to their predicted risk for overdose or suicide-related events or death in the next year (45); the tool, however, currently accesses only VA data.

This study has several limitations. First, it relies on death certificate data generated through unstandardized overdose investigations that may produce data of varied quality and accuracy across states (46, 47). We do not believe that any misclassification of cause of death or specific drugs identified would differ across the exposure groups. Illicit fentanyl could also be reported as a prescription opioid under ICD-10 code T40.4; however, we believe that such misattribution would be minimal because deaths involving synthetic fentanyl became predominant in most U.S. regions after our study period (48). Second, because of the age of the data, our findings may not accurately reflect contemporary effect estimates; however, the fundamental relationship between dual use of opioids and deaths from prescription opioid overdose may not have changed. Third, our study focused on unintentional deaths, limiting the generalizability of our findings to patients whose overdose deaths were intentional or due to illicit opioids, such as heroin. Whether our findings would generalize to other types of dual health care system use by nonveterans is also unknown (49). Fourth, we could not identify any opioid prescriptions obtained outside VA or Medicare Part D, such as those paid for in cash or by other insurance or obtained through illicit purchases. We also could not determine whether opioids were consumed as prescribed. Finally, despite matching case to control patients on several measured demographic and clinical characteristics and regression adjustment for other important covariates, we cannot rule out residual confounding. A limitation in our estimation of the magnitude of a confounding variable needed to nullify the observed association is that it may not be applicable in the context of multiple confounders. However, the extent of confounding would have to be impractically large to nullify the magnitude of the association between dual receipt of opioids and death from prescription opioids.

Among veterans dually enrolled in VA and Medicare Part D, receipt of prescription opioids from both systems was associated with more than 2 to 3 times the odds of unintentional death from prescription opioid overdose than with receipt of opioids from only 1 system. These results emphasize the relevance of identifying this vulnerable group of veterans and the importance of care coordination across providers and health care systems to increase the safety of opioid prescribing both inside and outside VA.

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Appendix: Description of ICD-10 Codes Used to Identify Case Patients Who Died of Unintentional or Undetermined-Intent Prescription Opioid Overdose

X42: Accidental poisoning by and exposure to narcotics and psychodysleptics (hallucinogens), not elsewhere classified

OR

X44: Accidental poisoning by and exposure to other and unspecified drugs, medicaments, and biological substances

OR

Y12: Poisoning by and exposure to narcotics and psychodysleptics (hallucinogens), not elsewhere classified, undetermined intent

OR

Y14 - Poisoning by and exposure to other and unspecified drugs, medicaments, and biological substances, undetermined intent

AND

T40.2 - Poisoning by, adverse effect of, and underdosing of other opioids

OR

T40.3 - Poisoning by, adverse effect of, and underdosing of methadone

OR

T40.4 - Poisoning by, adverse effect of, and underdosing of other synthetic narcotics.

Appendix Table 1. Association Between Source of Opioid Prescriptions and Unintentional or Undetermined-Intent Death From Prescription Opioid Overdose in Veterans Enrolled in Both VA and Medicare Part D Among Case and Control Patients Matched Within Facility

Source of Opioid Prescriptions (*N* = 727)	Case Patients (*N* = 166), *n* (%)	Control Patients (*N* = 561), *n* (%)	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)*	*P* Value
VA only	36 (21.7)	193 (34.4)	1.00 (reference)		1.00 (reference)	
Part D only	90 (54.2)	293 (52.2)	1.75 (1.10–2.77)	0.018	1.69 (1.04–2.73)	0.033
Dual use	40 (24.1)	75 (13.4)	3.12 (1.80–5.43)	<0.001	2.82 (1.57–5.04)	<0.001
Dual use vs. Part D only	NA	NA	1.79 (1.12–2.87)	0.016	1.67 (1.02–2.74)	0.043

NA = not applicable; OR = odds ratio; VA = U.S. Department of Veterans Affairs.
* Adjusted for patient demographic characteristics, including age, marital status, prescription drug monitoring program operational status, and medication use ≤180 d before the index date (antidepressants, antipsychotics, and total number of nonopioid drugs).

Appendix Table 2. Comparison of Association Between Source of Opioid Prescriptions and Unintentional or Undetermined-Intent Death From Prescription Opioid Overdose in Models With or Without Adjustment for Opioid Dosage, Gabapentin or Pregabalin, and Benzodiazepine Use

Source of Opioid Prescriptions	Case Patients (*N* = 215), *n* (%)	Control Patients (*N* = 833), *n* (%)	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)*	*P* Value	Adjusted OR (95% CI)†	*P* Value
VA only	42 (19.5)	279 (33.5)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Part D only	113 (52.6)	437 (52.5)	1.73 (1.17–2.57)	0.006	1.93 (1.26–2.95)	0.002	2.14 (1.34–3.41)	0.002
Dual use	60 (27.9)	117 (14.0)	3.36 (2.13–5.29)	<0.001	3.53 (2.17–5.75)	<0.001	3.33 (1.97–5.62)	<0.001
Dual use vs. Part D only	NA	NA	1.94 (1.31–2.86)	<0.001	1.83 (1.20–2.77)	0.005	1.56 (0.97–2.51)	0.069

NA = not applicable; OR = odds ratio; VA = U.S. Department of Veterans Affairs.
* This set of adjusted results (as well as the raw data and unadjusted results) is from the primary analyses presented in Table 2. Adjusted for patient demographic characteristics, including age, marital status, prescription drug monitoring program operational status, and medication use ≤180 d before the index date (antidepressants, antipsychotics, and total number of nonopioid drugs).
† Additionally adjusted for days with opioid supply, average daily morphine milligram equivalents, days with morphine milligram equivalents >120, gabapentin and pregabalin, and any overlap in use of benzodiazepines and opioids.

Appendix Table 3. Association Between Source of Opioid Prescriptions and Unintentional or Undetermined-Intent Death From Prescription Opioid Overdose in Veterans Enrolled in Both VA and Medicare Part D Among Fee-for-Service Enrollees

Source of Opioid Prescriptions	Case Patients (*N* = 155), *n* (%)	Control Patients (*N* = 599), *n* (%)	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)*	*P* Value	Adjusted OR (95% CI)†	*P* Value
VA only	32 (20.6)	216 (36.1)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Part D only	79 (51.0)	305 (50.9)	1.75 (1.11–2.77)	0.017	2.06 (1.26–3.36)	0.004	2.01 (1.19–3.43)	0.010
Dual use	44 (28.4)	78 (13.0)	3.69 (2.17–6.26)	<0.001	4.28 (2.41–7.58)	<0.001	4.04 (2.11–7.74)	<0.001
Dual use vs. Part D only	NA	NA	2.11 (1.32–3.36)	0.002	2.08 (1.26–3.43)	0.004	2.00 (1.14–3.53)	0.016

NA = not applicable; OR = odds ratio; VA = U.S. Department of Veterans Affairs.
* Adjusted for patient demographic characteristics, including age, marital status, prescription drug monitoring program operational status, and medication use ≤180 d before the index date (antidepressants, antipsychotics, and total number of nonopioid drugs).
† Adjusted for alcohol and substance use disorder diagnoses, and comorbid conditions and health service use measures from the Risk Index for Overdose or Serious Opioid-Induced Respiratory Depression (diagnosis of cancer, chronic hepatitis or cirrhosis, bipolar disorder or schizophrenia, chronic pulmonary disease, end-stage renal disease, active traumatic injury, or sleep apnea, any hospitalization, or any emergency department visit), in addition to previously mentioned covariates.

Appendix Table 4. Association Between Source of All Prescriptions (Not Only Opioids) and Unintentional or Undetermined-Intent Death From Prescription Opioid Overdose in Veterans Enrolled in Both VA and Medicare Part D

Source of Any Prescriptions	Case Patients (*N* = 215), *n* (%)	Control Patients (*N* = 833), *n* (%)	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)*	*P* Value
VA only	27 (12.5)	199 (23.9)	1.00 (reference)		1.00 (reference)	
Part D only	67 (31.2)	283 (34.0)	1.83 (1.11–3.01)	0.018	2.19 (1.27–3.76)	0.005
Dual use	121 (56.3)	351 (42.1)	2.75 (1.72–4.41)	<0.001	3.19 (1.93–5.28)	<0.001
Dual use vs. Part D only	NA	NA	1.51 (1.06–2.15)	0.024	1.46 (0.99–2.17)	0.059

NA = not applicable; OR = odds ratio; VA = U.S. Department of Veterans Affairs.
* Adjusted for patient demographic characteristics, including age, marital status, prescription drug monitoring program operational status, and medication use ≤180 d before the index date (antidepressants, antipsychotics, and total number of nonopioid drugs).