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Receipt of Overlapping Opioid and Benzodiazepine Prescriptions among Veterans Dually Enrolled in Medicare Part D and VA

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Abstract

Background: Overlapping opioid and benzodiazepine use is associated with increased risk of overdose. Veterans receiving medications concurrently from VA and Medicare may be at higher risk of such overlap.

Objective: To assess the association between dual use of VA and Medicare drug benefits and receipt of overlapping opioid and benzodiazepine prescriptions.

Design: Cross-sectional

Setting: VA and Medicare

Participants: All Veterans enrolled in VA and Part D filling ≥ 2 opioid prescriptions in 2013 (n=368,891).

Measurements: Two outcome measures: the proportion of patients with (1) a Pharmacy Quality Alliance (PQA) measure of opioid/benzodiazepine overlap (i.e., 2 fills for benzodiazepines with 30days overlap with opioids); or (2) high-dose opioid/benzodiazepine overlap (i.e., 30days overlap with daily opioid dosage >120 MME). We used augmented inverse probability weighting regression to compare these measures by source of prescription drugs: VA-only, Part D-only, or VA and Part D (Dual use).

Results: Of the 368,891 eligible Veterans, 18.3% received all their prescriptions from VA only, 30.3% from Medicare only, and 51.4% from both VA and Medicare. The proportion with PQA opioid/benzodiazepine overlap was larger for the dual use group versus the VA only (23.1% vs. 17.3%, adjusted risk ratio (aRR) = 1.27, 95%CI 1.24–1.30) and Medicare only (23.1% vs. 16.5%, aRR 1.12, 95%CI 1.10–1.14) groups. The proportion with high-dose overlap was also larger for the dual use group versus the VA only (4.7% vs. 2.3%, aRR = 2.23, 95%CI 2.10–2.36) and Medicare only (4.7% vs. 2.9%, aRR=1.06, 95%CI 1.02–1.11) groups.

Limitations: Data are from 2013

Conclusions: Among a national cohort of Veterans dually enrolled in VA and Medicare, receiving prescriptions from both sources was associated with a greater risk of receiving potentially unsafe overlapping opioid and benzodiazepine prescriptions.

INTRODUCTION

Concurrent use of prescription opioids and benzodiazepines is associated with an increased risk of overdose and death. In a study from the US Department of Veterans Affairs (VA), Veterans concurrently prescribed both types of medications had more than twice the risk of overdose death, and this risk increased among patients prescribed higher benzodiazepine doses(1). Other studies conducted among non-Veterans have corroborated an association between concomitant opioid/benzodiazepine use and overdose death(2–7). In addition, non-benzodiazepine hypnotics (such as zolpidem, eszopiclone, and zaleplon) may also increase risk of opioid overdose, particularly among those with anxiety or post-traumatic stress disorder(6,8–10).

Against the backdrop of rapidly increasing rates of death due to opioid overdose(6,11,12), this growing body of evidence led several organizations to formalize recommendations against widespread concomitant use of opioids and benzodiazepines. Concurrent usage is now cautioned against by opioid product labeling(13), VA guidelines(14), and CDC opioid prescribing guidelines(12). CDC guidelines also recommend that daily opioid dosages not exceed 90 morphine milligram equivalents (MME) and that use of opioids with other

sedating medications be assessed carefully for risks and benefits(12). Opioid and benzodiazepine overlap is now measured by the Pharmacy Quality Alliance (PQA)(15). This PQA opioid/benzodiazepine overlap measure is being tracked by the Centers for Medicare and Medicaid Services (CMS) as of January 1, 2018(16).

Among Veterans cared for in the VA Healthcare System, clinical assessment of concurrent opioid and benzodiazepine use can be complicated by co-prescribing from outside VA, as a large majority of Veterans are enrolled in other forms of health insurance. For example, more than 30% of VA-enrolled Veterans are co-enrolled in Medicare Part D(17). The use of two or more healthcare systems (“dual system use”) can result in poorly coordinated care that increases the risk of prescribing errors. Dual system use has been associated with potentially unsafe medication prescribing among patients with dementia(18), unnecessary utilization of healthcare resources(19,20), increased unsafe opioid prescribing(21–23), and increased risk of rehospitalization following stroke(24), among other adverse outcomes(25–28). Although use of prescription drug monitoring programs is routinely recommended to assess opioid prescribing across payers(12), less attention has been paid to benzodiazepine prescriptions, alone or in combination with other medications. For example, there is no current or planned requirement in most U.S. states that prescribers check a prescription drug monitoring program when they prescribe a benzodiazepine, and local rules regarding monitoring opioid prescriptions have historically varied widely by state(29).

The purpose of this study was to assess the association between receiving medications from both VA and Medicare Part D (dual use) and the receipt of overlapping opioid and benzodiazepine prescriptions. We hypothesized that dual use would increase the risk of such potentially unsafe prescribing.

METHODS

Data Sources

We linked comparable data from VA and CMS at the patient level. We obtained relevant VA data from the VA Pharmacy Benefits Management Services, which retains data on all prescriptions dispensed to VA patients, and the VA Corporate Data Warehouse, which contains data on patient demographics, encounters (including inpatient, outpatient, and skilled nursing care), and diagnosis codes. We obtained CMS data on inpatient and skilled nursing facility stays from the Medicare Provider Analysis and Review file (MedPAR); enrollment and sociodemographic data from the CMS Beneficiary Summary File; diagnoses from the MedPAR, home health, hospice, outpatient, and carrier files; and dispensed prescriptions from the Medicare Part D prescription drug event files.

Study Sample and Dual Use Definition

We identified all patients enrolled in both VA and Medicare Part D in calendar year 2013 (CY13) who filled at least one opioid from either source, including Medicare fee-for-service and managed care enrollees (n=654,578). Opioids used in the analyses are listed in eTable 4; sublingual buprenorphine formulations were not used in cohort construction. We excluded 13,454 (2.1%) patients for whom milligram morphine equivalent dosage (MME) could not

be calculated for one or more of the opioids received (e.g., for certain oral liquid dosage forms). We also excluded an additional 29,410 (4.5%) patients who received hospice or palliative care services (15). The primary outcome measure (described below) was constructed using the PQA definition of opioid/benzodiazepine overlap, which requires that patients have at least 2 opioid prescriptions filled on at least 2 separate days for at least 15 total days' supply in a year (15). Thus, we excluded patients who either had only one opioid prescription filled (199,129; 30.4%), did not reach a total of 15 days' supply of opioids (43,694; 6.7%), or both. Cohort construction is detailed in Figure 1.

The final cohort was categorized by the source of each patient's prescription medications in CY13 (including all medications, not simply opioids or benzodiazepines), which we refer to as "dual use status." Patients who received all of their medications only from VA sources were deemed "VA only." Those who received all of their medications only from Medicare Part D were deemed "Medicare only," and those who received at least one prescription medication (of any kind, not simply opioids or benzodiazepines) from both sources were deemed "dual users." Dual use status was the primary exposure of interest.

Study Outcomes

We combined Medicare Part D data and VA Pharmacy Benefits Management dispensing data to identify all opioids and benzodiazepines dispensed to patients retained in the cohort in CY13. MME was calculated for all opioids using conversions from the Centers for Disease Control (CDC), in a manner similar to prior analyses(21,30). We assumed every prescription dispensed started on the date of dispensing and covered a number of days equal to its days' supply. Exposures to opioids, benzodiazepines, and sedatives (operationally defined below) were coded for each day in CY13.

We examined two primary outcomes. The first was the percentage of patients meeting the PQA definition of opioid/benzodiazepine overlap. PQA overlap is present when a patient receives 2 or more prescriptions for benzodiazepines filled on 2 or more days with at least 30 days of opioid overlap(15). The second outcome examined the percentage of patients with high-dose opioid (>120 MME)/benzodiazepine overlap for at least 30 days, without restriction on the number of benzodiazepine prescriptions. The 120 MME cutoff is used by PQA in its operationalization of high-dose opioid use; this threshold has been adopted in an assessment of provider quality by the National Committee on Quality Assurance(15, 31). We wanted to identify not only concurrent opioid/benzodiazepine use, but also concurrent use in which the opioid dosage was high, as this infers increased risk of overdose and death(12). In a sensitivity analysis described below, we also defined high-dose opioid/benzodiazepine overlap using the CDC threshold of >90 MME(12) as the cut point instead of >120 MME.

In secondary analyses, we combined benzodiazepines and the sleep aids eszopiclone, zaleplon, and zolpidem into a group operationally defined as sedatives. We then examined the number and percentage of patients who were exposed to an opioid and an overlapping sedative for at least 30 days, or exposed to >120 MME daily opioid dose with an overlapping sedative for at least 30 days.

Primary Variables and Covariates

The primary independent variable of interest was each patient's medication dual use status (VA only, Medicare only, or dual use) in CY13. Covariates were identified in a manner consistent with previous work on dual enrollment and high-dose opioid prescribing and chosen based on factors believed to impact either dual use status or use of opioids and benzodiazepines(21). Demographic variables included age, sex, and race/ethnicity. Race/ethnicity was primarily assessed using VA data; if VA data were missing, the Medicare race/ethnicity variable was used instead(32). We incorporated markers of socioeconomic status or need for healthcare services, including disability insurance benefits as the reason for initial Medicare enrollment and enrollment in Medicaid and/or low-income subsidies (LIS). We also included an indicator for HMO enrollment status in CY13. Geographic data was encoded by capturing the ZIP code of patient residence in CY13 from Medicare. This ZIP code was then used with the CY13 Area Health Resource File to obtain an Urban Influence Code (UIC), a measure of rurality used by the U.S. Department of Agriculture's Economic Research Service(33). We also used ZIP codes to approximate driving distance to the nearest VA primary care clinic, and U.S. Census region (South, West, Northeast, Midwest, or outside the 50 United States and Washington D.C.).

We also considered the number of distinct drugs prescribed, excluding benzodiazepines and opioids, to adjust for comorbidity(34), in a manner consistent with previous analyses(35). We also captured presence or absence of any outpatient prescription fill for skeletal muscle relaxants, non-benzodiazepine sleep aids (the "z drugs" eszopiclone, zaleplon, and zolpidem), antidepressants, antipsychotics, alcohol dependence medications, and buprenorphine/naloxone; a full list of medications used is in eTable 2). As in a prior analysis(21), these medications were chosen as proxies for selected diagnoses (e.g., depression), as International Classification of Diseases, Ninth Edition (ICD-9) diagnosis codes from Medicare are not available for Medicare managed care enrollees and our goal was to include all Medicare Part D enrollees in the main analyses. In a sensitivity analysis, we repeated all analyses on the subgroup of fee-for-service Medicare beneficiaries, for whom diagnosis data were available, and risk adjusted using ICD-9-based health status indicators, including the number of Elixhauser comorbidities(37) in the prior year, pain or cancer diagnoses, and substance use disorder.

ANALYSIS

We summarized and compared patient characteristics across the three prescription source groups using chi-squared tests for categorical variables and analysis of variance tests or Kruskal-Wallis tests for continuous variables. We also calculated and compared the percentage of patients with each outcome using chi-squared tests. To examine associations between extent of fragmentation in medication supply and opioid/benzodiazepine overlap, we plotted the relationship between the proportion of prescriptions (measured by total days of supply of medications) provided by VA (as opposed to Medicare Part D) against the percentage of patients with the two outcomes (PQA overlap and high-dose opioid/benzodiazepine overlap).

To account for potential selection bias based on differences in observable characteristics across prescription source groups, we used augmented inverse probability weighting (AIPW) to assess the adjusted association between prescription source group and opioid/benzodiazepine overlap. AIPW is a doubly robust method that combines regression adjustment and inverse-probability-weighted methods. First, inverse probability of treatment weights were developed using multinomial logistic regression to estimate the probability of belonging to each dual use status group; then, weighted multivariable logistic regression was used to model the outcomes across prescription source groups, using the covariates described above(38). We assessed the balance of covariates between groups using standardized difference, where a value <0.1 is considered negligible(39). We used Stata procedure *teffect* (*Treatment-effects estimation for observation study*) with logit link to estimate the adjusted probabilities for direct comparison of dual use status groups, and then used nonlinear combination (nlcom) to estimate the adjusted risk ratios (aRRs). Presence of non-benzodiazepine sedatives (eszopiclone, zaleplon, and zolpidem) was retained as a covariate when adjusting for benzodiazepine overlap, but not when adjusting for overall sedative overlap. Difference in percentages, risk ratios, and 95% confidence intervals were calculated. With only 0.3% missing data across all variables, we used complete-case analysis by removing those records in multivariable models.

We conducted two sensitivity analyses to assess the robustness of our estimates. First, we redefined high-dose opioid /benzodiazepine overlap using >90 MME, a value consistent with CDC guidelines(12), as a cut point instead of >120 MME. Second, we repeated all analyses on the subgroup of fee-for-service Medicare beneficiaries, for whom ICD-9 based health status indicators are available. We adjusted for the number of Elixhauser comorbidities(37) and presence of substance use disorder diagnoses in the prior year (2012), and for ICD-9-based indicators of pain or cancer diagnoses throughout CY13.

Analyses were carried out using SAS version 9.4 (SAS Institute Inc, Cary NC) and StataMP 15. Approval was obtained from the Institutional Review Board at the VA Pittsburgh Healthcare System.

RESULTS

The final cohort consisted of 368,891 patients enrolled in both VA and Medicare Part D who received at least 2 opioid prescriptions on at least 2 separate days with more than 15 days total exposure in CY13. The mean age of the entire cohort was 70.2, with approximately 72% being 65 years of age or older. Most of the cohort was male (96.1%) and non-Hispanic white (79.2%; Table 1). In the final cohort, 67,472 (18.3%) received prescriptions only from VA (the “VA only” group), 111,641 (30.3%) received prescriptions only from Medicare Part D (“Medicare only”), and 189,778 (51.4%) received one or more prescriptions from both sources (“dual use”).

Compared to Veterans receiving medication from VA only, Veterans with dual use were slightly older, more likely to be white, were prescribed a larger number of unique medications, were less likely to be eligible for both Medicaid and low-income subsidies, and were less likely to have a disability as the original reason for Medicare enrollment (Table 1).

Additional information regarding comorbidities among the subgroup of Medicare fee-for-service enrollees can be found in eTable 3.

Unadjusted Overlap by Dual Use Status

Overall, 27.8% of Veterans had at least one day of opioid/benzodiazepine overlap, with an average of 36.4 days overlap among all Veterans analyzed. The dual use group had the highest proportion with any overlap (31.4%) and the greatest number of days of overlap (mean 43.2) ($P<0.001$). A similar pattern was observed when measuring days of overlap between opioids and all sedatives (Table 2).

PQA-defined opioid/benzodiazepine overlap occurred in 17.3% of VA only users, 16.5% of Medicare only users, and 23.1% of dual users ($P<0.001$) (Table 2). High dose opioid/benzodiazepine overlap for ≥ 30 days occurred in 2.3% of VA only users, 2.9% of Medicare only, and 4.7% of dual users ($P<0.001$). Similar patterns across prescription source groups were seen when examining opioid overlap with sedatives, with higher rates of ≥ 30 days of opioid/sedative overlap and ≥ 30 days of high dose opioid/sedative overlap in the dual use group (Table 2).

Extent of Dual Use and Degree of Overlap

Figure 2 details the relationship between the proportion of all prescriptions provided by VA and the percentage of patients with either PQA overlap or high-dose opioid/benzodiazepine overlap. The relationships followed a dose-response pattern, with greater rates of overlap as prescriptions were more evenly split between VA and Part D, and less overlap when prescriptions were received primarily from one system. Overlap was most prevalent with approximately 60% VA use/40% Medicare Part D use, in which 26.7% had PQA overlap and 6.6% had high dose opioid/benzodiazepine overlap (Figure 2).

Adjusted Analyses of Overlap by Dual Use Status

After adjustment, all standardized differences across dual use groups in the propensity-score weighted model were less than 0.1 (eTable 4). Dual users were more likely to have PQA opioid/benzodiazepine overlap than VA only users (aRR=1.27, 95% CI 1.24, 1.30) and Medicare only users (aRR=1.12, 95% CI 1.10, 1.14) (Table 3). Dual users were also more likely to have high dose opioid/benzodiazepine overlap than VA only users (aRR=2.23, 95% CI 2.10, 2.36) and Medicare only users (aRR=1.06, 95% CI 1.02, 1.11); similar adjusted associations were present when examining overlapping opioids and sedatives (eTable 5), or when the high dose opioid cutoff was set to >90 MME (eTable 6).

The sensitivity analysis of fee-for-service Medicare enrollees ($n=198,276$), with additional adjustment for comorbidities using ICD-9 codes, produced similar results (eTable 7). Dual use was associated with higher risk of PQA opioid/benzodiazepine overlap when compared to VA only use (aRR=1.29, 95% CI 1.25, 1.33) or Medicare only use (aRR=1.08, 95% CI 1.06, 1.11). High-dose opioid/benzodiazepine overlap was twice as likely in dual users when compared to VA only users (aRR=2.23, 95% CI 2.09, 2.39). The distinction between dual users and Medicare only users with respect to high-dose opioid/benzodiazepine overlap was no longer present after adjustment (aRR=0.98, 95% CI 0.93, 1.04) (eTable 7).

DISCUSSION

In a national cohort of Veterans dually enrolled in VA and Medicare Part D who received an opioid from one of these systems, receiving prescription medications from both VA and Medicare Part D was associated with a 27% increased risk of overlapping opioids and benzodiazepines and more than twice the risk of overlapping high dose opioids with benzodiazepines, compared to receiving prescriptions from VA alone. Receipt of prescriptions from both VA and Medicare was also associated with a greater risk of opioid/benzodiazepine overlap compared to Medicare alone, although the magnitude of the difference was smaller. As VA and Medicare work to mitigate the risks from prescription opioids, these findings suggest that receipt of medications from more than one health care system is a key risk factor for unsafe prescribing practices.

These results are compatible with the findings of other recent observational studies that identify the risks associated with concomitant VA and non-VA care. Dual prescribing of medications has been associated with greater risk of receiving potentially unsafe medications in the elderly with dementia(18) and greater risk of receiving high-dose, long duration prescription opioids(21). Another study conducted within a single statewide prescription drug monitoring program found 3-fold larger odds of overlapping opioid/benzodiazepine use among Veterans with dual sources of prescriptions(23). In contrast to our analyses, this study used only one day of concomitant prescriptions to define overlap and only adjusted for sex and age. Our additional finding of a dose-response relationship between the proportion of prescriptions provided by VA and Medicare and two robust measures of opioid/benzodiazepines overlap extends the prior work and supports the contention that care fragmentation among dual users contributes to potentially unsafe prescribing practices.

It is particularly troubling that rates of overlapping opioid and benzodiazepines in which the opioid dosage was very high (>120MME) were twice as common among dual users compared to VA only use. High opioid dosages alone are a risk factor for adverse events, including overdose, and are a major focus of quality improvement efforts around opioids and the CDC opioid prescribing guidelines.(12) Opioid/benzodiazepine co-prescribing is similarly a target of CDC and VA guidelines.(12, 14) However, the combination of high opioid dosage and benzodiazepine overlap has not been explicitly addressed in these guidelines, even though the risks of combining these medications are magnified at such high opioid dosages.(3) Despite the low rates of high dose opioid/benzodiazepine overlap in our sample, the substantially increased risk among dual users requires attention.

While the VA's electronic health record system can make prescribers aware of diagnoses and treatments from other VA facilities, the system does not routinely capture and report non-VA system use. The VA's Opioid Safety Initiative and other opioid safety programs now track opioid/benzodiazepine dispensing but use VA data only (40). Prescription drug monitoring databases across the nation provide an additional measure of decisional support. However, the onus still falls on providers to manually check these databases, as they are not yet incorporated into the electronic health records within VA. Such integration could build upon an automated notification system that has been correlated with a reduction in concomitant

opioid/benzodiazepine prescribing in a VA quality improvement project(41). Though many physicians are now mandated to check prescription drug monitoring programs before issuing opioid prescriptions, this is not the case for benzodiazepine prescriptions; this is especially problematic in situations where individuals receive prescriptions through unconnected health care systems and/or payers, as in VA and non-VA dual use.

This study has important limitations. First, our data do not capture medications purchased without insurance or illicitly, and consequently may underestimate the actual frequency of opioid/benzodiazepine overlap. Second, temporal trends (such as the VA's Opioid Safety Initiative or recent improvements in submission of VA prescription data to state PDMPs)(40) may have affected concomitant opioid/benzodiazepine use since the time frame of our study. Nonetheless, these data represent the first national assessment of opioid/benzodiazepine overlap across health systems within either VA or Medicare. Third, despite the robust statistical methods applied, the potential for unmeasured confounding remains in this cross-sectional study. Regardless of the causal relationship, however, our findings clearly document that dual medication prescribing is a key marker of greater risk of opioid/benzodiazepine overlap. Fourth, the study was restricted to patients eligible to meet the PQA definition of opioid/benzodiazepine overlap (i.e., those with at least 2 opioid prescriptions and at least 15 total days of exposure in 2013) and to Veterans enrolled in Medicare Part D, which limits the generalizability of our study findings. Finally, our analysis focused on process measures of prescribing safety and did not capture medical outcomes, such as overdose or death.

In conclusion, among a national cohort of Veterans dually enrolled in VA and Medicare Part D, receiving prescription medications from both sources was associated with a greater risk of receiving potentially unsafe overlapping opioids and benzodiazepines compared to receiving prescriptions from either source alone. These findings highlight the need to enhance coordination of care across health care systems to optimize the quality and safety of prescribing.

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Figure 1.
cohort construction

Note: The percentage of days supply of medication received from VA includes all medications, and not only prescription opioids or benzodiazepines. For example, of individuals with 80-90% of their total days supply from VA (and 10-20% from Part D), 24.5% had PQA opioid/benzodiazepine overlap. Individuals at 100% of total days supply from VA thus receive all their medications from VA and none from Part D.

Figure 2.

The percentage of veterans with opioid/Benzodiazepine overlap by the percentage of Days Supply of Medications obtained from VA

Table 1.
Patient Characteristics for Prescription Opioid Recipients Enrolled in VA and Medicare Part D in CY13

Characteristics	All	Prescription Source *		
		VA Only	Medicare Only	Dual Use
	368,891	67,472	111,641	189,778
		18.3%	30.3%	51.4%
Age, years, mean (sd)	70.2 (11.1)	66.1 (10.5)	74.0 (10.6)	69.4 (10.9)
Age, years, %				
18–39	0.7	1.0	0.3	0.7
40–64	27.6	42.3	15.9	29.2
65–84	60.5	51.4	65.3	60.9
85+	11.3	5.2	18.5	9.2
Male, %	96.1	95.4	96.6	96.0
Race, %				
Hispanic	4.9	5.9	3.5	5.4
Non-Hispanic White, single race	79.2	69.5	86.8	78.2
Non-Hispanic Black, single race	13.8	22.2	7.9	14.3
Non-Hispanic Other	2.1	2.4	1.9	2.2
Disability as reason for Medicare enrollment, %	45.0	57.8	31.2	48.7
Medicaid and Low Income Subsidy (LIS) enrolled 2013, %				
Medicaid eligible	26.4	37.2	23.4	24.3
Medicaid ineligible/LIS eligible	6.5	12.6	4.0	5.9
Medicaid ineligible/LIS ineligible	67.1	50.3	72.6	69.8
Region, %				
South	43.4	43.9	38.9	45.8
West	20.1	23.0	21.4	18.4
Northeast	13.4	10.4	16.6	12.5
Midwest	21.7	21.4	22.6	21.3
Outside the 50 States and outside DC	1.4	1.4	0.5	2.0

Characteristics	All	Prescription Source *		
		VA Only	Medicare Only	Dual Use
Urban Influence: %				
Large Metropolitan	41.7	42.0	43.6	40.5
Small Metropolitan	36.3	36.1	34.8	37.4
Micropolitan	12.3	12.3	12.0	12.4
Noncore Rural	9.7	9.6	9.7	9.7
Driving distance to nearest VA Primary Care clinic, miles, median (Q1-Q3)	12 (6-23)	10 (5-22)	12 (6-23)	12 (6-23)
Medication use in CY13, %				
Benzodiazepines	30.3	22.0	28.9	34.1
Skeletal Muscle relaxants	24.4	27.1	17.5	27.4
Sleep aids	13.3	9.2	13.0	15.0
Antidepressants	42.6	43.4	36.5	45.9
Antipsychotics	9.7	11.1	7.8	10.4
Alcohol dependence medications	0.2	0.3	0.1	0.2
Buprenorphine/naloxone	0.3	0.1	0.1	0.4
Total non-opioid, non-benzodiazepine drugs, mean (sd)	12.0 (5.9)	11.1 (5.6)	10.4 (5.3)	13.3 (6.0)

* Prescription source is defined based on all medications (not limited to opioids and benzodiazepines) and categorized as: VA only: received all prescriptions from VA. Medicare only: received all prescriptions from Medicare. Dual use: received at least one prescription from each source.

Abbreviations: CY13, Calendar year 2013; VA, Department of Veterans Affairs; LIS, Low-income subsidy

Numbers represent column percents unless otherwise specified

All p-value for comparing patient characteristics across the 3 groups were <0.001

Missing data: race (n=646); region (n=571); UIC (n=587); driving (n=79). No other values were missing.

Table 2.

Prevalence of Prescription Opioid/Benzodiazepine and Opioid/Sedative Overlaps among Dually Enrolled Veterans Receiving a Prescription Opioid in 2013, by Source of Prescription Medicines

Overlap Measure	Opioid/Benzodiazepine Overlap				Opioid/Sedative * Overlap			
	Total	VA Only	Medicare **	Dual Use **	Total	VA ** Only	Medicare ** Only	Dual Use **
	n=368,891	n=67,472	n=111,641	n=189,778	n=368,891	n=67,472	n=111,641	n=189,778
Any overlap, n (%)	102,450 (27.8)	14,047 (20.8)	28,795 (25.8)	59,608 (31.4)	128,863 (34.9)	18,047 (26.7)	36,742 (32.9)	74,074 (39.0)
Days of overlap, mean (sd)	36.4 (84.6)	33.6 (88.4)	27.6 (71.9)	43.2 (93.2)	47 (93.7)	43.2 (93.2)	36.8 (81.7)	54.3 (99.7)
30 days of overlap, n (%)	76,556 (20.8)	11,940 (17.7)	19,280 (17.3)	45,336 (23.9)	98,837 (26.8)	15,500 (23.0)	25,551 (22.9)	57,786 (30.4)
PQA Opioid/Benzodiazepine Overlap *** , n (%)	73,967 (20.1)	11,691 (17.3)	18,408 (16.5)	43,868 (23.1)	N/A	N/A	N/A	N/A
30 days of overlap with MME>120 **** , n(%)	13,714 (3.7)	1,550 (2.3)	3,229 (2.9)	8,935 (4.7)	16,374 (4.4)	1,876 (2.8)	3,904 (3.5)	10,594 (5.6)

Abbreviations: PQA, Pharmacy Quality Alliance; MME, morphine milligram equivalents; VA, Department of Veterans Affairs

*“Sedatives” include benzodiazepines and non-benzodiazepine sleep aids (the “z drugs” eszopiclone, zaleplon, and zolpidem).

** Prescription source is defined based on all medications and categorized as: VA only: received all prescriptions from VA. Medicare only: received all prescriptions from Medicare. Dual use: received at least one prescription from each source.

*** PQA opioid/benzodiazepine overlap present when a patient receives 2 benzodiazepine prescriptions on 2 days with 30 days of overlap with opioids in a calendar year. PQA does not have an analogous opioid/sedative overlap measure so we show 30 days of opioid/sedative overlap.

**** Overlapping opioid and benzodiazepine prescriptions when the opioid dosages is >120 MME.

Table 3.

Adjusted Associations between Source of Medication, defined as VA only, Medicare only, and Dual VA-Medicare, and Overlap Measures (n=368,891)

Comparison	PQA Overlap		High-Dose Opioid/Benzodiazepine Overlap for 30 Days	
	Risk Ratio (95% CI)	Difference in Percentages* (95% CI)	Risk Ratio (95% CI)	Difference in Percentages* (95% CI)
Dual VA-Medicare Use vs. VA-only Use				
Unadjusted	1.33 (1.31, 1.36)	5.8% (5.5%, 6.1%)	2.05 (1.94, 2.16)	2.4% (2.3%, 2.6%)
IPW adjustment**	1.27 (1.24, 1.30)	4.7% (4.3%, 5.0%)	2.23 (2.10, 2.36)	2.4% (2.3%, 2.6%)
Dual VA-Medicare Use vs. Medicare-only Use				
Unadjusted	1.40 (1.38, 1.42)	6.6% (6.3%, 6.9%)	1.63 (1.56, 1.69)	1.8% (1.7%, 2.0%)
IPW adjustment**	1.12 (1.10, 1.14)	2.3% (2.0%, 2.6%)	1.06 (1.02, 1.11)	0.3% (0.1%, 0.5%)

PQA, Pharmacy Quality Alliance; VA, Department of Veterans Affairs; IPW, inverse probability weighting

* Percentage point difference between groups

** Covariates: age; gender; race; 2013 HMO enrollment; disability; 2013 Medicaid and low-income subsidy; state; Urban Influence Code; driving distance to nearest VA primary care; use of sleep aids, muscle relaxants, antidepressants, antipsychotics, alcohol dependence medications, and buprenorphine/naloxone; and number of non-opioid and non-benzodiazepine drugs prescribed in 2013; n=367,651

eTable 1.

Medication Names Used to Identify Opioids

Medication Use Class
Buprenorphine *
Codeine
Dihydrocodeine
Fentanyl
Hydrocodone
Hydromorphone
Levorphanol
Meperidine
Methadone
Morphine
Opium
Oxycodone
Oxymorphone
Pentazocine
Propoxyphene
Remifentanyl
Sufentanyl
Tapentadol
Tramadol

* Transdermal formulation only

eTable 2.**Medications Used to Construct Medication Use Classes**

Medication Use Class	Medications	
Benzodiazepines	1. Alprazolam 2. Chlordiazepoxide 3. Clobazam 4. Clonazepam 5. Clorazepate 6. Diazepam 7. Estazolam 8. Flurazepam	9. Halazepam 10. Lorazepam 11. Midazolam 12. Oxazepam 13. Prazepam 14. Quazepam 15. Temazepam 16. Triazolam
Muscle Relaxants	1. Carisoprodol 2. Chlorzoxazone 3. Cyclobenzaprine 4. Metaxalone 5. Methocarbamol	6. Orphenadrine 7. Tizanidine 8. Baclofen 9. Chlorphenesin 10. Dantrolene
Sleep Aids	1. Butabarbital 2. Eszopiclone 3. Ramelteon	4. Zaleplon 5. Zolpidem
Antidepressants	1. Amitriptyline 2. Amoxapine 3. Bupropion 4. Citalopram 5. Clomipramine 6. Desipramine 7. Desvenlafaxine 8. Doxepin 9. Duloxetine 10. Escitalopram 11. Fluoxetine 12. Fluvoxamine	13. Imipramine 14. Maprotiline 15. Mirtazapine 16. Nefazodone 17. Nortriptyline 18. Paroxetine 19. Phenelzine 20. Protriptyline 21. Sertraline 22. Tranylcypromine 23. Trimipramine 24. Venlafaxine
Antipsychotics	1. Chlorpromazine 2. Chlorprothixene 3. Clozapine 4. Fluphenazine 5. Haloperidol 6. Loxapine 7. Mesoridazine 8. Molindone 9. Olanzapine	10. Paliperidone 11. Perphenazine 12. Pimozide 13. Quetiapine 14. Risperidone 15. Thioridazine 16. Thiothixene 17. Trifluoperazine 18. Ziprasidone
Alcohol Dependence Medications	1. Acamprosate 2. Disulfiram	3. Naltrexone
Buprenorphine/Naloxone	1. Buprenorphine/Naloxone	

Medications

Medication Use Class

eTable 3.
Additional Diagnosis Information for Prescription Opioid Recipients Enrolled in VA and Medicare Fee-for-Service

Characteristics	All	Prescription Source		
		VA Only	Medicare Only	Dual Use
	198,276	41,148	63,840	93,288
Percent of Fee-for-Service Enrollees, %	100	20.8	32.2	47.0
Pain diagnosis in CY13, %	80.3	69.1	79.8	85.5
Cancer diagnosis in CY13, %	16.9	8.8	21.5	17.4
Substance use diagnosis in CY12, %	14.1	20.1	7.7	15.9
Number of Elixhauser comorbidities at baseline (2012), mean (SD)	2.9 (2.5)	2.4 (2.1)	2.9 (2.6)	3.1 (2.5)

eTable 4:

Standardized Differences between Patient Characteristics for VA Only vs Dual Use And Part D Only vs Dual Use, Before (Raw) and After (Weighted) Propensity Score Weighting

Standardized Differences*	VA Only vs. Dual Use		Part D Only vs. Dual Use		Part D Only vs. VA only	
	Raw	Weighted	Raw	Weighted	Raw	Weighted
Age, years, %						
40–64	0.276	0.047	–0.323	0.005	–0.609	–0.042
65–84	–0.191	–0.031	0.091	–0.005	0.283	0.026
85+	–0.153	–0.021	0.274	–0.001	0.421	0.020
Male, %	–0.032	–0.015	0.032	–0.006	0.064	0.008
Race, %						
Non-Hispanic White, single race	0.207	0.037	–0.205	0.000	–0.409	–0.037
Non-Hispanic Black, single race	0.023	0.008	–0.094	–0.005	–0.117	–0.013
Non-Hispanic Other	0.014	0.007	–0.026	0.000	–0.039	–0.007
Disability as reason for Medicare enrollment, %	0.184	0.062	–0.363	0.007	–0.556	–0.055
Medicare HMO enrollment	–0.240	0.072	–0.161	0.001	0.078	–0.071
Medicaid and Low Income Subsidy (LIS) enrolled 2013, %						
Medicaid ineligible/LIS eligible	0.231	0.006	–0.091	0.037	–0.317	0.031
Medicaid ineligible/LIS ineligible	–0.408	–0.013	0.062	–0.064	0.473	–0.051
Urban Influence, %						
Small Metropolitan	–0.026	0.004	–0.054	–0.005	–0.029	–0.008
Metropolitan	–0.003	0.004	–0.012	0.005	–0.009	0.002
Noncore Rural	–0.003	0.001	–0.001	0.008	0.002	0.007
Driving distance to nearest VA Primary Care clinic, miles, median (Q1–Q3)	–0.057	0.068	0.021	0.010	0.069	–0.063
Medication use in CY13, %						
Sleep aids	–0.179	–0.002	–0.060	0.004	0.119	0.006
Skeletal Muscle relaxants	–0.007	0.033	–0.241	0.000	–0.234	–0.033
Antidepressants	–0.052	0.008	–0.193	–0.015	–0.140	–0.023

Standardized Differences*	VA Only vs. Dual Use		Part D Only vs. Dual Use		Part D Only vs. VA only	
	Raw	Weighted	Raw	Weighted	Raw	Weighted
Antipsychotics	0.023	0.011	-0.092	-0.018	-0.114	-0.029
Alcohol dependence medications	0.004	-0.001	-0.038	-0.002	-0.042	-0.001
Buprenorphine/naloxone	-0.059	0.005	-0.054	0.000	0.005	-0.004
Total non-opioid, non-benzodiazepine drugs, mean (sd)	-0.377	0.012	-0.524	0.013	-0.142	0.001

* State is not listed in above due to number of categories; all states had standardized difference of <0.10.

Note: Sample size of the multivariable models: n=367,651. 1240 (0.3%) patients were removed due to missing data.

Abbreviations: CY13, Calendar year 2013; VA, Department of Veterans Affairs; LIS, Low-income subsidy

Adjusted Associations between Source of Medications and Opioid/Benzodiazepine or Sedative Overlap

eTable 5.

Comparison	Overlap Measures		High-Dose Opioid Overlap Measures	
	Risk Ratio (95% CI)	Difference in Percentages* (95% CI)	Risk Ratio (95% CI)	Difference in Percentages* (95% CI)
	PQA Opioid/Benzodiazepine Overlap		High-Dose Opioid/Benzodiazepine Overlap for 30 Days	
Dual VA-Medicare Use vs. VA-only Use				
Unadjusted	1.33 (1.31, 1.36)	5.79% (5.45%, 6.13%)	2.05 (1.94, 2.16)	2.41% (2.26%, 2.56%)
IPW adjustment**	1.27 (1.24, 1.30)	4.65% (4.27%, 5.02%)	2.23 (2.10, 2.36)	2.42% (2.28%, 2.56%)
Dual VA-Medicare Use vs. Medicare-only Use				
Unadjusted	1.40 (1.38, 1.42)	6.62% (6.34%, 6.92%)	1.63 (1.56, 1.69)	1.82% (1.68%, 1.95%)
IPW adjustment**	1.12 (1.10, 1.14)	2.29% (1.95%, 2.63%)	1.06 (1.02, 1.11)	0.27% (0.08%, 0.45%)
	Opioid/Sedative Overlap for 30 Days		High-Dose Opioid/Sedative Overlap for 30 Days	
Dual VA-Medicare Use vs. VA-only Use				
Unadjusted	1.33 (1.31, 1.35)	7.48% (7.10%, 7.86%)	2.01 (1.91, 2.10)	2.80% (2.64%, 2.96%)
IPW adjustment***	1.28 (1.26, 1.30)	6.31% (5.91%, 6.72%)	2.21 (2.09, 2.32)	2.85% (2.69%, 3.00%)
Dual VA-Medicare Use vs. Medicare-only Use				
Unadjusted	1.33 (1.31, 1.35)	7.56% (7.24%, 7.88%)	1.60 (1.54, 1.65)	2.09% (1.94%, 2.23%)
IPW adjustment***	1.08 (1.07, 1.10)	2.20% (1.83%, 2.57%)	1.04 (1.00, 1.08)	0.21% (0.004%, 0.41%)

PQA, Pharmacy Quality Alliance; VA, Department of Veterans Affairs; IPW, inverse probability weighting

* Percentage point difference between groups

** Covariates: age; gender; race; 2013 HMO enrollment; disability; 2013 Medicaid and low-income subsidy; state; Urban Influence Code; driving distance to nearest VA primary care; use of sleep aids, muscle relaxants, antidepressants, antipsychotics, alcohol dependence medications, and buprenorphine/naloxone; and number of non-opioid and non-benzodiazepine drugs prescribed in 2013; N=367,651

*** Covariates: age; gender; race; 2013 HMO enrollment; disability; 2013 Medicaid and low-income subsidy; state; Urban Influence Code; driving distance to nearest VA primary care; use of muscle relaxants, antidepressants, antipsychotics, alcohol dependence medications, and buprenorphine/naloxone; and number of non-opioid and non-sedative drugs prescribed in 2013; N=367,651

eTable 6.

Adjusted Associations between Sources of Medication and High-Dose Opioid/Benzodiazepine Overlap, Using Different Thresholds of High Opioid Dosage

Comparison	>120 MME/Benzodiazepine Overlap for 30 Days (Primary Analysis)		>90 MME/Benzodiazepine Overlap for 30 Days (Sensitivity Analysis)	
	Risk Ratio (95% CI)	Difference in Percentages (95% CI)	Risk Ratio (95% CI)	Difference in Percentages (95% CI)
Dual VA-Medicare Use vs. VA-only Use				
Unadjusted	2.05 (1.94, 2.16)	2.4% (2.3%, 2.6%)	1.96 (1.88, 2.05)	3.0% (2.9%, 3.2%)
IPW adjustment**	2.23 (2.10, 2.36)	2.4% (2.3%, 2.6%)	2.10 (1.99, 2.21)	3.0% (2.9%, 3.2%)
Dual VA-Medicare Use vs. VA-only Use				
Unadjusted	1.63 (1.56, 1.69)	1.8% (1.7%, 2.0%)	1.68 (1.62, 1.73)	2.5% (2.3%, 2.7%)
IPW adjustment**	1.06 (1.02, 1.11)	0.3% (0.1%, 0.5%)	1.11 (1.07, 1.16)	0.6% (0.4%, 0.8%)

PQA, Pharmacy Quality Alliance; VA, Department of Veterans Affairs; IPW, inverse probability weighting; MME, Morphine Milligram Equivalent

* Percentage point difference between groups

** Covariates: age; gender; race; 2013 HMO enrollment; disability; 2013 Medicaid and low-income subsidy; state; Urban Influence Code; driving distance to nearest VA primary care; use of sleep aids, muscle relaxants, antidepressants, antipsychotics, alcohol dependence medications, and buprenorphine/naloxone; and number of non-opioid and non-benzodiazepine drugs prescribed in 2013; N=367,651

eTable 7:

Associations between Source of Medications and Opioid/Benzodiazepine or Sedative Overlap among Fee-for-Service Medicare Enrollees

Comparison	Overlap Measures		High-Dose Opioid Overlap Measures	
	Risk Ratio (95% CI)	Difference in Percentages* (95% CI)	Risk Ratio (95% CI)	Difference in Percentages* (95% CI)
PQA Opioid/Benzodiazepine Overlap				
Dual VA-Medicare Use vs. VA-only Use				
Unadjusted	1.41 (1.38, 1.44)	7.2% (6.8%, 7.7%)	2.24 (2.09, 2.39)	3.1% (2.9%, 3.3%)
IPW adjustment**	1.29 (1.25, 1.33)	5.1% (4.6%, 5.7%)	2.23 (2.05, 2.41)	2.8% (2.6%, 3.0%)
Dual VA-Medicare Use vs. Medicare-only Use				
Unadjusted	1.40 (1.37, 1.43)	7.1% (6.7%, 7.5%)	1.69 (1.61, 1.77)	2.3% (2.1%, 2.5%)
IPW adjustment**	1.08 (1.06, 1.11)	1.8% (1.3%, 2.3%)	0.98 (0.93, 1.04)	-0.1% (-0.4%, 0.2%)
Opioid/Sedative Overlap for 30 Days				
Dual VA-Medicare Use vs. VA-only Use				
Unadjusted	1.39 (1.36, 1.42)	9.1% (8.6%, 9.6%)	2.16 (2.03, 2.29)	3.5% (3.3%, 3.8%)
IPW adjustment***	1.29 (1.26, 1.33)	6.9% (6.3%, 7.5%)	2.18 (2.02, 2.33)	3.2% (3.0%, 3.5%)
Dual VA-Medicare Use vs. Medicare-only Use				
Unadjusted	1.32 (1.30, 1.34)	7.9% (7.5%, 8.4%)	1.64 (1.57, 1.71)	2.58% (2.4%, 2.8%)
IPW adjustment***	1.05 (1.03, 1.07)	1.5% (1.0%, 2.0%)	0.96 (0.91, 1.01)	-0.2% (-0.5%, 0.1%)

PQA, Pharmacy Quality Alliance; VA, Department of Veterans Affairs; IPW, inverse probability weighting

* Percentage point difference between groups

** Covariates: age; gender; race; disability; 2013 Medicaid and low-income subsidy; state; Urban Influence Code; driving distance to nearest VA primary care; use of sleep aids, muscle relaxants, antidepressants, antipsychotics, alcohol dependence medications, and buprenorphine/naloxone; number of non-opioid and non-benzodiazepine drugs prescribed in 2013; number of Elixhauser conditions (excluding drugs and alcohol); and diagnosis codes for pain or cancer in CY13. N=197,680