Concurrent Use of Opioids and Benzodiazepines in a Medicare Part D Population

May 12, 2016

Background

Since 1999, the amount of prescription opioids sold in the U.S. nearly quadrupled, as did deaths from prescription opioids.[1] In 2010, the Administration released its first National Drug Control Strategy, noting that overdoses from opioids is a "growing national crisis". [2] The Centers for Disease Control and Prevention (CDC)[3] reported that opioids were associated with the most pharmaceutical-related overdose deaths in 2010 (75.2%), followed by benzodiazepines (29.4%). In addition, benzodiazepines use was associated with 30.1% of opioid overdose deaths and opioid use was associated with 77.2% of benzodiazepine overdose deaths. Benzodiazepines, such as alprazolam are prescription drugs classified as Central Nervous System (CNS) depressants. These drugs work by inhibiting brain activity that can produce a drowsy or calming effect. This property makes them useful in the treatment of anxiety, sleep disorders, and seizures but also can depress an individual's respiratory system. Consequently, concurrent use of benzodiazepines with other CNS depressants, such as opioids, can place an individual at an increased risk for severe respiratory depression that can lead to death. These adverse events can occur in both patients that do and do not exhibit signs of drug abuse. Although, the recent CDC guidelines on opioid prescribing in chronic non-cancer pain advises clinicians to avoid co-prescribing opioids and benzodiazepines whenever possible[4], others are calling for stronger warnings.

According to the Washington Post, health officials across the US are encouraging the Food and Drug Administration (FDA) to warn people about the potential dangers of taking opioid pain medications along with benzodiazepines. In a petition, officials from 41 state and municipal health departments, as well as some universities, "urged the agency" to add boxed warnings to both medications, "given evidence that using them together increases the chance of deadly overdoses." In a statement, the FDA said it "is committed to working with the health care community and our federal, state and local partners to help reduce opioid and benzodiazepine misuse and abuse."[5] On March 22, 2016, the FDA announced its intent to develop enhanced warnings and safety information for immediate-release (IR) opioid labeling including risks due to interactions with CNS depressants.[6]

Issue

The purpose of the analysis is to quantify the concurrent use of opioids and benzodiazepines among Medicare Part D enrollees.

Methods

Measurement Period:

January 1, 2015 to December 31, 2015.[7]

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[1] CDC. Wide-ranging online data for epidemiologic research (WONDER). Atlanta, GA: CDC, National Center for Health Statistics; 2016. Available at http://wonder.cdc.gov.

[2] National Drug Control Strategy. https://www.whitehouse.gov/sites/default/files/ondcp/policy-and-research/ndcs2010_0.pdf.

[3] Jones CM, Mack KM, Paulozzi LJ. Pharmaceutical Overdose Deaths, United States, 2010 JAMA. 2013; 309(7):657-659. doi:10.1001/jama.2013.272.

[4] CDC Guideline for Prescribing Opioids for Chronic Pain. http://www.cdc.gov/drugoverdose/prescribing/guideline.html.

[5] Dennis, Brady. Health officials push FDA to add 'black box' warnings about using opioids, benzodiazepines together. Washington Post, February 22, 2016. Web. May 2, 2016.

[6] FDA News Release. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm491739.htm.

[7] Data pulled on March 3, 2016.

Study Design: Observational retrospective.

Concurrent Use Rates: The concurrent use rate calculation was adapted from the Pharmacy Quality Alliance (PQA)-endorsed specifications for the Drug-Drug Interaction measure which measures the percentage of beneficiaries who received a prescription for a target medication during the measurement period and who were dispensed a concurrent prescription for a precipitant medication.

- Calculate the rate of concurrent use of opioids and two groups of precipitant drugs:
  - Benzodiazepines (BZD) only
  - Benzodiazepines or non-benzodiazepine sedative/hypnotics (BZD-SH)

Numerator: Number of enrolled beneficiaries who were dispensed an opioid medication with at least one day overlap with a precipitant medication fill during the measurement period.

Denominator: Number of enrolled beneficiaries who were dispensed an opioid medication during the measurement period.

Prescribers most likely assess the risk and benefit of a medication differently for populations with specific co-morbidities. Prescribers may determine that the benefit of prescribing a BZD and/or BZD-SH to a patient receiving opioids may outweigh the risk of an adverse event in patients at the end of life or with a terminal illness. We therefore created three populations by excluding beneficiaries enrolled in hospice care alone and those in hospice care and/or a diagnoses of cancer.

- Calculate concurrent use rates for three populations.
  - All Part D beneficiaries
  - All Part D beneficiaries excluding beneficiaries enrolled in hospice
  - All Part D beneficiaries excluding beneficiaries enrolled in hospice or with a cancer diagnosis

- Stratify rates by organization type (PDP, MA-PD), low-income subsidy (LIS) status, age-groups, and disability.

- Calculate the number of concurrent events per beneficiary. Events are identified using the dates of service and days supply of a beneficiary's opioid and precipitant prescription drug claims. An event begins on the first day of overlapping days supply for an opioid and a precipitant drug claim. The event continues during all consecutive days of overlapping days supply, and ends on the first subsequent day where there is no overlapping days supply (i.e., the beneficiary may have only opioid days supply, only precipitant drug days supply, or neither drug). For example, a beneficiary with one event for 365 concurrent days, had opioid and precipitant drug fills that overlapped on every day of the year.

- Examine the most prevalent concurrent opioid-BZD combinations at the Medi-Span Generic Product Identifier (GPI) 10 drug name level in which given combinations occurred at least once.

Distributions:

- Beneficiary concurrent usage (days) stratified by one vs. multiple events.
- Number of events per beneficiary (Not shown).

Data Sources:

- Prescription Drug Event (PDE) Data – Identify opioid, BZD, and non-BZD claims.
- Risk Adjustment Processing System (RAPS) 2014 – Identify enrollees with cancer diagnoses.
- Common Medicare Environment (CME) – Identify contract enrollment and demographics.
- Enrollment Database (EDB) – Identify hospice enrollees.
- Medi-Span Master Drug Data Base (MDDB®) – Create National Drug Code (NDC) lists for opioids, benzodiazepines, and non-benzodiazepine sedative/hypnotics.

Target NDC Drug Lists:

- Opioids: Created based on a list of opioid medications obtained from the Centers for Disease Control and Prevention (CDC) that excludes cough & cold, injectable formulations, and buprenorphine products used to treat opioid use disorder.
- Precipitant medications, BZD or BZD-SH are based on following PQA list:
  - Benzodiazepines (BZD):

alprazolam	diazepam	midazolam
chlordiazepoxide	estazolam	oxazepam
clobazam	flurazepam	quazepam
clonazepam	halazepam	temazepam
clorazepate	lorazepam	triazolam

  - Non-Benzodiazepines Sedative/Hypnotics (SH):

eszopiclone	zaleplon	zolpidem

Results

Table 1 describes the number of Part D enrollees in each population, along with the number and percent receiving opioids, BZDs and BZD-SHs in 2015.

The total number of Part D enrollees decreased following the exclusions for hospice enrollment and then cancer diagnoses by 2.5% and 8.6%, respectively. Opioid use in the Part D population slightly decreased following each exclusion from 33.8% to 33.3%. BZD use dropped from 17.6% to 17.3%, while BZD-SH use was overall about 3 percentage points higher than the BZD only use within Part D enrollees. BZD-SH use decreased from 20.7% in the Part D population to 20.3% in the non-hospice and non-cancer Part D population.

Table 1. Number and Percent of Opioid, BZD and BZD-SH Users in each Part D Population, CY 2015

Populations	Part D Enrollees	Change in Part D Popn.	Opioid Users		BZD Users		BZD-SH Users	
	#	%	#	%	#	%	#	%
All	41,835,016		14,131,824	33.8%	7,379,173	17.6%	8,643,070	20.7%
Non-Hospice	40,774,748	-2.5%	13,690,914	33.6%	7,100,330	17.4%	8,341,752	20.5%
Non-Hospice and/or Non-Cancer	38,242,284	-8.6%	12,753,301	33.3%	6,629,621	17.3%	7,779,021	20.3%

Overall, opioid, BZD only, and BZD-SH use was very consistent across all populations, therefore, the results presented below are limited to the non-hospice and non-cancer Part D population.

Table 2 illustrates the rates of concurrent use of opioids and the two precipitant drug groups (BZD and BZD-SH) stratified by sponsor and enrollee characteristics.

Table 2. Opioid and BZD or BZD-SH Concurrent Usage in a non-Hospice and non-Cancer Part D Population, CY 2015

				Part D Opioid Users			
Population	Part D Enrollees	Opioid Users		Concurrent Opioid and BZD		Concurrent Opioid and BZD-SH Use	
Characteristics	#	#	As %	#	As %	#	As %
All	38,242,284	12,753,301	33.3%	3,062,764	24.0%	3,558,870	27.9%
Organization Type							
PDP	23,800,534	8,166,304	34.3%	2,047,860	25.1%	2,398,101	29.4%
MA-PD	15,364,486	4,988,100	32.5%	1,133,783	22.7%	1,296,562	26.0%
LIS Status							
Non-LIS	26,118,556	7,674,864	29.4%	1,511,298	19.7%	1,802,127	23.5%
LIS	12,123,728	5,078,437	41.9%	1,551,466	30.6%	1,756,743	34.6%
Age Group							
Under 65	6,943,220	3,390,321	48.8%	1,235,604	36.4%	1,402,239	41.4%
65 - 74	17,718,252	5,209,226	29.4%	1,041,921	20.0%	1,241,788	23.8%
75 - 84	9,414,509	2,908,457	30.9%	544,837	18.7%	641,721	22.1%
85 - up	4,166,303	1,245,297	29.9%	240,402	19.3%	273,122	21.9%
Current Medicare Enrollment Reason							
Aged/ESRD only	31,366,374	9,395,498	30.0%	1,834,333	19.5%	2,165,623	23.0%
Disabled w/wo ESRD	6,875,910	3,357,803	48.8%	1,228,431	36.6%	1,393,247	41.5%

- Overall, between 8-9% of Part D enrollees use opioids concurrently with BZDs or BZD-SHs (not shown). Concurrent use among Part D enrollee opioid users ranged from 24.0% for opioids and BZDs to 27.9% for opioids and BZD-SHs.

- Only small differences in concurrent opioid and BZD rates were observed between those enrolled in PDPs (25.1%) and MA-PDs (22.7%). Use of BZD-SHs increased the opioid concurrent rate by 3.3 to 4.3 percentage points. The MA-PD contracts continued to have a lower rate than the PDP contracts (26.0% vs. 29.4%).
- Although the absolute numbers of Non-LIS concurrent users differ by about 40,000 enrollees, the rate of concurrent opioid and BZD use was over 50% higher for LIS opioid users compared to Non-LIS [(30.6% - 19.7%)/19.7% = 55.3%]. When SH use was included, the concurrent use rate for both LIS and Non-LIS increased by about 4 percentage points, and the difference between the LIS and Non-LIS rate was reduced to slightly less than 50% [(34.6%-23.5%)/23.5% = 47.2%].
- A much greater difference in opioid and BZD concurrent use was observed in those under age 65 years (36.4%) compared to the older age groups (18.7% to 20.0%). This was also true with concurrent opioid and BZD-SH rates. Overall the opioid and BZD-SH concurrent rates were 2.6 to 5.0 percentage points higher than the opioid and BZD concurrent rate
- The opioid and BZD concurrent rate among the disabled (i.e., current Medicare enrollment reason is disabled and disabled with ESRD) was almost double that of the nondisabled (i.e., current Medicare enrollment reason is aged or ESRD alone) opioid users (36.6% vs 19.5%). A similar difference was observed with the opioid and BZD-SH concurrent rate (23.0% and 41.5%).
- Adjusting by member-years had a negligible effect on the rates.

Table 3 illustrates the distribution in deciles of concurrent days among users with one event. Deciles divide the population into 10 equal parts with each part representing 10% of the population. For example, for the distribution of concurrent usage (days) for opioids and BZDs among Part D opioid users with one event, 10% of the population with the lowest number of concurrent days used opioids and BZDs for two days or less. On the other hand, 10% of the population with the highest number of concurrent days used the drugs concurrently between 30 and 365 days (ranging from 90% to 'Max').

Approximately one-third of concurrent opioid and BZD users only had one concurrent consecutive-days event (992,369/3,062,764) and for 90% of these enrollees the number of days was 30 days or less. However, at least one beneficiary's single concurrent use lasted continuously for a full year. The concurrent days distributions were essentially the same for opioids and both precipitant drug groups; the mean number of concurrent days was only slightly different (single, 19.6 vs. 20.7).

Table 3. Distribution of Enrollee Concurrent Usage Days in a non-Hospice and non-Cancer Part D Population with One Event, CY 2015

Opioid and Precipitant Drug(s)	# of Events	Enrollee Count	Mean	10%	20%	30%	40%	50%	60%	70%	80%	90%	Max
BZD	One	992,369	19.6	2	3	4	5	7	10	15	23	30	365
BZD-SH	One	1,145,655	20.7	2	3	4	5	7	10	15	25	30	365

Alternately, over two-thirds of concurrent users had two or more events. The concurrent days distributions, shown in Table 4, was essentially the same for opioids and both precipitant drug groups (within 3 days). The mean days were almost the same (multiple, 147.9 vs. 147.1), the median was 120 and 122 days, and concurrent use ranged from two (not shown) to 364 days.

Table 4. Distribution of Enrollee Concurrent Usage Days in a non-Hospice and non-Cancer Part D Population with Multiple-Events, CY 2015

Opioid and Precipitant Drug(s)	# of Events	Enrollee Count	Mean	10%	20%	30%	40%	50%	60%	70%	80%	90%	Max
BZD	>1	2,070,395	147.9	18	35	58	86	122	171	224	275	316	364
BZD-SH	>1	2,413,215	147.1	18	35	58	85	120	168	222	275	316	364

Among enrollees with multiple concurrent events, over 50% of the population had high concurrent use of 120 or more days of either an opioid and BZD or BZD-SH. More than 30% of the multiple event population show evidence of long-term consistent concurrent use during 2015 (i.e., greater than 180 days).

Table 5 lists the most frequent combinations of opioids and BZDs by the number of events in 2015. The top three combinations are hydrocodone-acetaminophen (a short-acting opioid) along with alprazolam, lorazepam, or clonazepam.

Table 5. Top 10 Opioid and BZD Medication Combinations by Number of Concurrent Usage Events, in a non-Hospice and non-Cancer Part D Population, CY 2015

Opioid	Benzodiazepine	Number of Events
Hydrocodone and Acetaminophen	Alprazolam	2,258,342
Hydrocodone and Acetaminophen	Lorazepam	1,189,501
Hydrocodone and Acetaminophen	Clonazepam	1,183,348
Oxycodone and Acetaminophen	Alprazolam	843,144
Tramadol	Alprazolam	817,150
Hydrocodone and Acetaminophen	Diazepam	768,715
Oxycodone	Alprazolam	601,238
Tramadol	Lorazepam	579,536
Tramadol	Clonazepam	570,571
Oxycodone and Acetaminophen	Clonazepam	485,769
(all other combinations…)		6,210,929
Total		15,508,243

Note: Full tables are available upon request for both the complete Part D and non-hospice only populations.

Limitations

- Diagnosis of cancer is determined from the 2014 RXHCC, so enrollees diagnosed with new cancers in 2015 are included in the non-cancer population. Also, enrollees whose cancer was in remission or cured in 2015 are still identified as having cancer.
- Cancer prognosis is treated equally for anyone with the diagnoses regardless of the type of cancer or stage.

Summary

In the non-cancer or non-hospice enrolled Part D opioid user population, the prevalence of opioid and BZD concurrent use was 24% and when SHs were included, use increased to about 28% among Part D opioid users. This represents about 3.1 to 3.6 million Part D enrollees. The number of enrollees at risk increased by almost 17% when enrollees using SHs were included in the rate calculation. Concurrent use was higher among opioid

users under the age of 65 years, LIS eligible compared to Non-LIS eligible enrollees and within enrollees with a current Medicare enrollment reason of disability compared to those with enrollment reason of aged. The distribution of concurrent days were similar for both precipitant drug groups (BZD or BZD-SH) suggesting that the duration of use for both groups are similar among opioid users. Over 50% of opioid users (≈1.0 to 1.2 million) with multiple concurrent events had use that lasted over four months or were high chronic users and over 30% (between 620,000 to 720,000 enrollees) had concurrent use that lasted more than six months or very high concurrent users.

Discussion

Over 3 million Medicare Part D enrollees receive concurrent opioids and BZD-SH drug therapies, potentially increasing their risk of overdose and death, primarily due to respiratory depression. In 2015, over 1.0 million of the Medicare Part D concurrent users were considered high chronic users, with use lasting more than four months. In addition to the increased risk of overdose, there is evidence that long-term use of BZD is associated with cognitive impairment and that following withdrawal impairment can persist. Despite concerns surrounding the co-prescribing of opioids and benzodiazepines, the concurrent use is quite prevalent in Medicare Part D enrollees.

CMS is concerned with both the high prevalence of concurrent opioids and benzodiazepines therapy, as well as instances of very long durations of use. In the 2017 Final Call Letter, CMS discussed these concerns and encouraged Part D sponsors to evaluate their claims data and use available drug utilization management tools to help address the concurrent use of these drug classes.[8] Additional steps may include verification or documentation of appropriate diagnoses and treatment monitoring through claims review or case management, and the investigation of prescribers with a high number of concurrent users.

Also, we are aware that a measure concept, Double Threat: Concurrent Use of Opioids and Benzodiazepines, is in development by the PQA. CMS will continue to monitor concurrent use of opioids and benzodiazepines among Medicare Part D enrollees, especially egregious chronic high dose concurrent opioid and BZD-SH, and will analyze additional metrics for potential use in oversight or performance measurement of Part D sponsors.

[8] 2017 Announcement. https://www.cms.gov/Medicare/Health-Plans/MedicareAdvtgSpecRateStats/Announcements-and-Documents.html