Co-utilization of opioids and nonbenzodiazepine hypnotic drugs in U.S. ambulatory care visits, 2006–2016

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ABSTRACT

Objective(s): This study aimed to characterize the co-utilization of non-benzodiazepine sedative 'Z'-drugs with opioids at ambulatory care visits in the United States.
Design: A cross-sectional analysis of the National Ambulatory Medical Care Survey (NAMCS) from 2006 to 2016 was completed.
Setting and participants: Ambulatory care visits in the United States involving adult patients with an opioid prescription were included in the analysis.
Outcome measures: The primary outcome was initiation or continuation of a Z-drug (zolpidem, eszopiclone, or zaleplon) in a patient visit in conjunction with an opioid medication.
Results: The authors analyzed 564,090,296 visits (weighted from a sample of 28,773) with a reported opioid prescription. Co-utilization of opioids with Z-drugs fluctuated during the study period beginning at 4.0% in 2006 (95% CI 2.2%–5.7%), 6.3% in 2012 (3.7%–8.9%), and 4.7% in 2016 (2.8%–6.5%). Among all opioid visits in the study period, co-utilization with a Z-drug was not significantly different among female patients compared with male patients (5.26% vs. 4.63%, $P = 0.26$). Among visits with concomitant opioid and Z-drugs, 7.0% reported new initiation of both medications in the same visit.
Conclusion: At ambulatory care visits between 2006 and 2016, co-utilization of opioids and Z-drugs fluctuated with some differences by sex. Major regulatory advisories and policy changes during this period may have contributed to these varying rates of utilization. Additional work is needed to identify predictors of co-utilization and downstream consequences more widely.

Background

The consequences associated with opioid use, including overdose, have been augmented by the increased prevalence of their co-utilization with other medications with sedative properties such as benzodiazepines.[1] The Centers for Disease Control and Prevention guidelines published in 2016 warned against the concurrent prescribing of opioids and benzodiazepines, a class of sedatives often used to treat anxiety and insomnia.[2] Results from studies evaluating the additional risks associated with concomitant uses of these medications led U.S. Food and Drug Administration (FDA) to require a black box warning of serious risks and death associated with the combined use of opioid analgesics and benzodiazepines.[3]

Although a large body of evidence exists documenting the increased use and associated risks of the concurrent use of opioids with benzodiazepines, substantial gaps remain in the characterization of trends in outpatient use of opioids concurrently with a related class of sedative medications known as nonbenzodiazepine hypnotics, despite noted risks. Nonbenzodiazepine hypnotic drugs are frequently prescribed for the treatment of insomnia and include zolpidem, zopiclone, eszopiclone, and zaleplon, collectively known as "Z"-drugs.[4] Although structurally unrelated, nonbenzodiazepine hypnotic

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Key Points

Background:

- Major regulatory advisories and policy changes related to opioid and Z-drug prescribing were enacted within the last 15 years.
- Concomitant use of opioids and Z-drugs has been shown to increase the risk of opioid overdose.

Findings:

- From 2006 to 2016, 5.0% of U.S. outpatient visits that included an opioid prescription also included a prescription for a Z-drug. Rates of co-utilization of opioids and Z-drugs fluctuated throughout this period.
- New prescriptions for an opioid and Z-drug were initiated concurrently in an estimated 1.9 million outpatient visits from 2006-2016, demonstrating a potentially problematic prescribing practice given the risks of concomitant use.

drugs are pharmacodynamically similar to benzodiazepines suggesting comparable, expansive risk profiles. On their own, the use of Z-drugs has been associated with psychomotor impairment leading to an increased risk of falls and fractures in older adults[5,6] along with misuse, abuse, dependence, and withdrawal.[7] In combination with opioids, Z-drug use has been associated with an increased risk of opioid-related overdose.[8-11] Evidence includes a recent analysis of the IBM MarketScan database, which found that among prescription opioid users, concomitant treatment with Z-drugs was associated with a substantial, statisically significant increase in the risk of unintentional overdose compared with patients using only prescription opioids.[10]

Despite these known risks, there remains a gap in information about the trends in co-utilization of opioids with Z-drugs specifically, as Z-drugs are frequently grouped with other sedatives in published analyses. A previous study using the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey found no clear changes in the co-prescribing of opioids and sedative hypnotics (benzodiazepine, muscle relaxant, or Z-drug) over the period of 2001-2010; however, visits were restricted to those with a principal reason for the visit being musculoskeletal pain.[12] A 2019 analysis of the NAMCS by Peckham et al.[13] showed increasing rates of high-risk opioid prescribing, defined as an opioid prescribed with a benzodiazepine, barbiturate, or hypnotic, in the 2-year intervals spanning from 2006 to 2016. Neither study reported rates of opioid co-use specifically with Z-drugs.

Major regulatory advisories and changes in prescribing guidance over the past decade may have influenced the use and prescribing rates of Z-drugs and opioids, including the addition of eszopiclone, zaleplon, and zolpidem to the 2012 American Geriatrics Society's Beers Criteria, recommending avoidance of these Z-drugs in older adults with a history of falls or fractures or cognitive impairment and avoiding chronic use (>90) in all patients aged 65 years or older.[14] A 2015 update to the Beers Criteria provided even stricter recommendations, warning against the use of Z-drugs in all persons aged 65 years or older without consideration of the duration of use.[15] Other events included an FDA recommendation for lowered doses of zolpidem-containing products in 2013, the rescheduling of hydrocodone-containing products from a class III controlled substance to class II by the Drug Enforcement Administration (DEA) in 2014,[16] and FDA's addition of a boxed warning about the risk for serious injuries associated with zaleplon, zolpidem, and eszopiclone in April 2019.[17] This study was undertaken to address the existing gap in knowledge surrounding outpatient opioid and Z-drug co-utilization in the United States during this critical time frame.

Objective

This study aimed to assess the trends in the co-utilization of opioids and Z-drugs using ambulatory visits documented in the NAMCS, a nationally representative database, between 2006 and 2016.

Methods

Data source

This project used the NAMCS from 2006 to 2016. The NAMCS is an annual national probability sample survey of nonfederally employed, office-based physicians conducted in the United States by the Division of Health Care Statistics, National Center for Health Statistics.[18] The survey employs a multistage probability sampling design of county-like designations (primary sampling units), provider practices within primary sampling units, and patient visits within a practice.[19] The final sampling unit is the office-based physician visit. Each visit is assigned a weight depending on the primary sampling unit and the provider's practice type within each primary sampling unit, resulting in a data set that is representative of all outpatient, community-based office visits in a given year. The NAMCS collects information about each visit including patient demographics, diagnoses, medications, reasons for visit, and provider type, among other variables. The serial cross-sectional nature of the NAMCS allows for tracking of trends over time; however, participating physicians and patients vary from year to year, preventing longitudinal follow-up.

From 2006 to 2011, only up to 8 medications could be documented in a single patient visit in the NAMCS; this number was increased to 10 medications in 2012 and further to 30 medications in 2014. In all years analyzed in this study, only the first 8 medications were included to ensure that any change in medication use was not influenced by an increase in the number of medication fields within the survey.[18] A post hoc sensitivity analysis was also completed by including all listed medications. Data here represented prescription medications newly initiated or continued, and the prescription was considered as an appropriate proxy for utilization.

Study population

All visits in which the patient was aged 18 years or older and was initiated on or continued an opioid medication from 2006 to 2016 were included in this study. Opioid medications

were identified using Multum drug classification categories 060 or 191, corresponding with narcotic analgesics and narcotic analgesic combinations, respectively (Appendix 1).

Outcomes

The primary outcome was the initiation or continuation of a Z-drug in a patient visit in conjunction with an opioid medication. Z-drugs were limited to zolpidem, eszopiclone, and zaleplon. Prescriptions for trazodone, an antidepressant medication prescribed primarily as an off-label therapy for sleep disorders,[20] were additionally analyzed to measure trends in the prescribing of sleep medications more broadly. Unlike Z-drugs, trazodone is not classified as a controlled substance by U.S. DEA and has not been the subject of regulatory or safety warnings regarding its co-use with opioids. Respective generic codes and drug entry codes used to identify Z-drugs and trazodone are listed in Appendix 1.

Covariates

The covariates assessed for an association with the trends of co-utilization of opioid medications with Z-drugs included patient age, race and ethnicity (imputed by the NAMCS if missing from the visit), geographic region, source of payment, and whether the patient was established at the practice. Sex was assessed to measure the potential effects of a 2013 FDA safety announcement that recommended that the initial dosing of zolpidem products be lowered in women. Additional potential covariates that were analyzed included diagnoses of asthma, chronic obstructive pulmonary disease (COPD), depression, diabetes, hypertension, obesity, osteoporosis, and cancer.

Statistical analysis

Data analyzed were weighted to unbiased nationally representative estimates using the weights derived from the sampled visits within the NAMCS. To account for the complex survey design, survey analysis procedures were used.[21,22] A multivariable logistic regression model was used to evaluate the association between the use of an opioid prescription and a Z-drug prescription in a single office visit, while adjusting for the aforementioned variables included as covariates. All data were analyzed using survey analysis procedures using SAS version 9.4 (SAS Institute, Inc, Cary, NC). This study was considered exempt by the institutional review board of the University of Florida.

Results

Overall, 6,434,992,016 visits (weighted from a sample of 289,713 unweighted visits) were reported from 2006 to 2016 for patients aged 18 years and older (Table 1). Study analysis included 564,090,296 weighted visits over this period in which an opioid medication was initiated or continued, equating to 8.8% of all adult visits.

The number of total visits that initiated or continued a Z-drug over this period was 136,540,078 (2.1%). The use of opioids increased from 2006 (6.9% [95% CI 5.8%–8.1%]) to 2014 (12.7% [10.5%–14.9%]), followed by possible nonsignificant decreases in 2015 (10.5% [8.0%–12.9%]) and 2016 (10.1% [8.4%–11.9%]). There was minimal change in the use of Z-drugs, totaling 1.8% (1.4%–2.1%) in 2006 and 1.5% (1.1%–1.8%) in 2016 (Figure 1). Across all years in the study period, zolpidem comprised 85.0% of all Z-drug prescriptions.

Table 1
Characteristics of ambulatory care visits that included an opioid prescription in the NAMCS, 2006–2016

Characteristic	No. visits (%) (n = 564,090,296)
Year	
2006–2008	172,553,973 (30.6)
2009–2012	221,764,243 (39.3)
2013–2016	169,772,080 (30.1)
Sex	
Women	329,189,404 (58.4)
Men	234,900,892 (41.6)
Age, y	
18–34	73,743,873 (13.1)
35–49	145,888,428 (25.9)
50–64	187,938,696 (33.3)
≥ 65	156,519,299 (27.7)
Race	
White only, non-Hispanic	418,516,975 (74.2)
Black only, non-Hispanic	68,337,294 (12.1)
Hispanic	53,994,432 (9.6)
Other or Multiple	23,241,595 (4.1)
Payer	
Private	236,781,030 (42.0)
Medicare	174,780,920 (31.0)
Medicaid or CHIP	66,863,843 (11.9)
Worker's comp	15,691,950 (2.8)
Self-pay	34,131,310 (6.1)
Other[a]	35,841,243 (6.4)
Region	
Northeast	81,869,897 (14.5)
Midwest	113,952,381(20.2)
South	234,213,660 (41.5)
West	134,054,358 (23.8)
Comorbidities	
COPD	40,063,121 (7.1)
Hypertension	207,291,424 (36.7)
Depression	96,804,681 (17.2%)
Obesity	61,252,783 (10.9)
Osteoporosis	23,596,542 (4.2)
Asthma	40,014,279 (7.1)
Cancer	49,613,893 (8.8)
Patient established at office	498,741,396 (88.4)

Abbreviations used: CHIP, Children's Health Insurance Program; COPD, chronic obstructive pulmonary disease; NAMCS, National Ambulatory Medical Care Survey.
[a] Other = no charge, charity, blank, unknown, other.

Opioid visits during the study period that also included a Z-drug totaled 28,210,523, or 5.0% of opioid visits; zolpidem comprised 87.5% of all Z-drug use among opioid users. This exceeded co-utilization of an opioid with trazodone (2.4%). The unadjusted yearly rate of opioid co-utilization with a Z-drug fluctuated throughout the study period beginning at 4.0% in 2006 (2.2%–5.7%) and ending at 4.7% in 2016 (2.8%–6.5%). The highest point estimate for prevalence was reported in 2012 (6.3% [3.7%–8.9%]); however, in 2013, opioid co-utilization with Z-drugs dropped to 4.5%, whereas co-utilization with trazodone remained near its highest rates in the study period (Figure 2).

Analysis completed without restricting to the first 8 medications appeared to show greater rates of co-utilization of opioids with Z-drugs and trazodone compared with the restricted

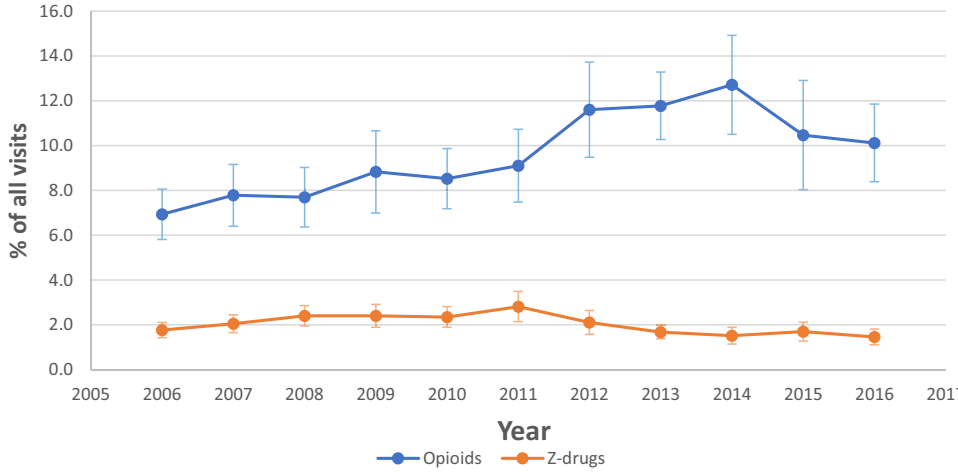

Figure 1. Unadjusted annual utilization rates of opioids and Z-drugs at all visits, 2006-2016. Error bars indicate 95% CIs.

analysis (Appendix 2) consistent with the expansion of medication fields in NAMCS to 10 in 2012 and to 30 in 2014. Still, changes in co-utilization did not differ significantly from year to year when included medication fields were unrestricted.

Sex stratification

Among all opioid visits in the study period, co-utilization with a Z-drug was not significantly different among female patients compared with male patients (5.26% vs. 4.63%, $P = 0.26$) (Figure 3). Changes in yearly co-utilization also differed nonsignificantly by sex, evidenced by overlapping 95% CIs. Co-utilization among women was potentially highest in 2009 (7.4% [2.5%–12.4%]) and lowest in 2015 (3.7% [2.2%–5.2%]), whereas co-utilization among males was potentially highest in 2012 (7.4% [4.0%–10.5%]) and lowest in 2010 (3.5% [2.0%–5.0%]).

New versus continued visits

Among 28,210,522 weighted visits that included both an opioid and Z-drug from 2006 to 2016, 1,968,961 (7.0%) of visits involved the new initiation of both drugs on the same day (Appendix 3). Among such visits with patients aged 65 years or older, the proportion in which both medications were newly initiated together was even lower at 2.4%, though this estimate was based on fewer than 30 raw visits.

Covariates/regression analysis

Opioid users who co-utilized Z-drugs differed from those who did not by age group ($P < 0.001$) and race ($P < 0.017$) (Table 2). Results of a multivariable logistic regression showed that opioid users aged 35-49 years (adjusted odds ratio 1.74 [95% CI 1.13–2.67]) and 50-64 years (2.39 [1.55–3.70]) were more likely to co-utilize an opioid and Z-drug compared with those aged 18-34 years. White, non-Hispanic opioid users were also more likely to co-utilize with a Z-drug than opioid users of other races when compared with black, non-Hispanic opioid users (1.61 [1.07–2.45]). Opioid visits in which patients self-paid were less likely to include co-utilization with a Z-drug compared with private payers (0.63 [0.41–0.95]). Visits among patients with COPD had a 49% reduction in co-utilization (0.51 [0.32–0.84]), whereas depression was associated with an 82% increased use in co-utilization (1.82 [1.42–2.33]).

Discussion

At opioid visits between 2006 and 2016, unadjusted rates of co-utilization with a Z-drug ranged from 4.0% in 2006 to 6.3% in 2009 and 2012; in 2016, the most recent dataset available, the rate was 4.7%. Year over year changes were mostly nonsignificant, as evidenced by overlapping 95% CIs. Rates of co-utilization of opioids with trazodone were lower relative to Z-drugs overall.

Opioid users with COPD had decreased odds of additionally using Z-drugs, a positive finding given the increased risk for adverse respiratory events with opioids, benzodiazepines, and opioids plus benzodiazepines use among older adults with COPD.[23] There were also reduced odds of co-utilization with Z-drugs among opioid users who self-paid compared with those with private insurance, an encouraging sign since uninsured individuals have reported higher rates of opioid misuse compared with the general U.S. population.[24]

Major regulatory advisories and policy changes may have had varying effects on rates of opioid and Z-drug use. After the approval of the first generic version of immediate-release zolpidem tartrate in April 2007,[25] co-utilization of Z-drugs and opioids increased steadily into 2009. A likely decrease in Z-drug use at opioid visits was seen between 2012 and 2013. A coinciding increase in the use of trazodone among opioid users from 2011 to 2014 could suggest that some Z-drug users were switched to another sleep drug. This aligns with an FDA safety announcement published in January 2013 that recommended that initial dosing of zolpidem products be lowered in women and cautioned of next-morning impairment that could occur in all patients.

The dangers of the concomitant use of opioids and benzodiazepines have resulted in FDA requiring its most prominent warning, a boxed warning, on these medications' prescribing information. The pharmacodynamic similarities between benzodiazepines and Z-drugs lead these medication classes to possess comparable, expansive risk profiles and both

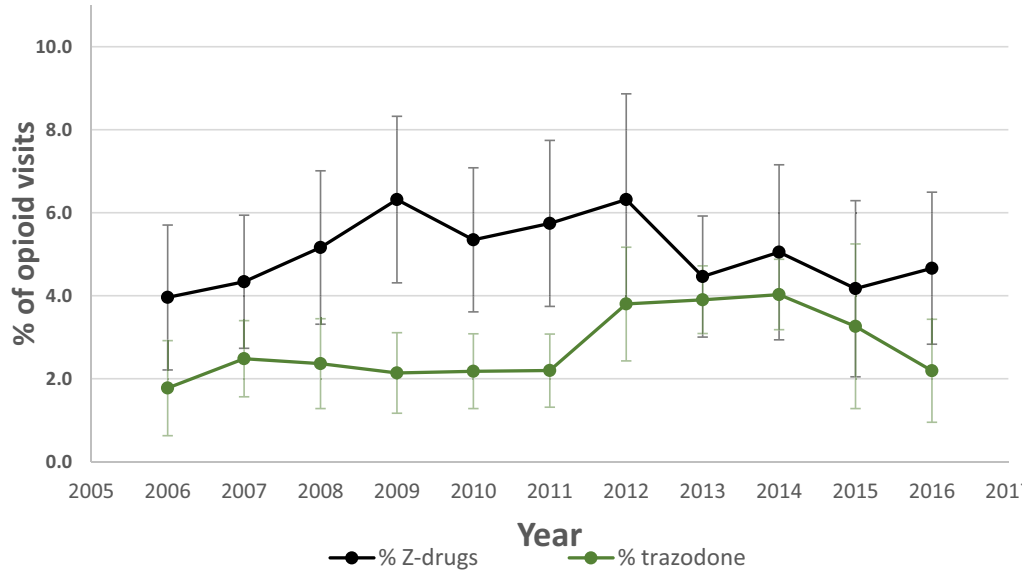

Figure 2. Trends in unadjusted opioid co-utilization with Z-drugs or trazodone, 2006-2016. Error bars indicate 95% CIs.

carry increased risk of respiratory depression when combined with opioids.[26,27] This analysis suggests that a portion of study visits included new initiation of both of an opioid and a Z-drug in a single visit. As the dangers of such co-utilization have been made evident, this prescribing practice is problematic as adverse events typically occur soon after initiation and, therefore, are compounded when both are initiated simultaneously.[28] A complex relationship exists between pain and insomnia, and initiating patients on potentially dangerous concomitant therapy could ultimately expose them to additional harm. Moreover, disruptions in patients' sleep patterns may result from inadequately controlled pain, so it may be more clinically prudent to delay the initiation of a Z-drug until the underlying cause of a patient's sleep disturbances is carefully evaluated and treated.[29]

Pharmacists and other health professionals can play key roles in preventing unnecessary co-utilization and potential adverse outcomes. In addition to avoiding concomitant initiation of opioids and Z-drugs, clinicians should be vigilant in regularly reassessing the appropriateness of such concomitant use in patients. Results of this study revealed that opioid users aged 35-64 years are more likely than those aged 18-34 years to also use Z-drugs; practitioners should thus be aware that this demographic is at risk of co-utilization and its associated dangers not merely older adults. Furthermore, clinicians can provide patients with thorough education on the risks of co-use, such as respiratory depression, and dispense naloxone when appropriate.

There were also strengths and limitations. The study population was not restricted by diagnosis code or reason for visit

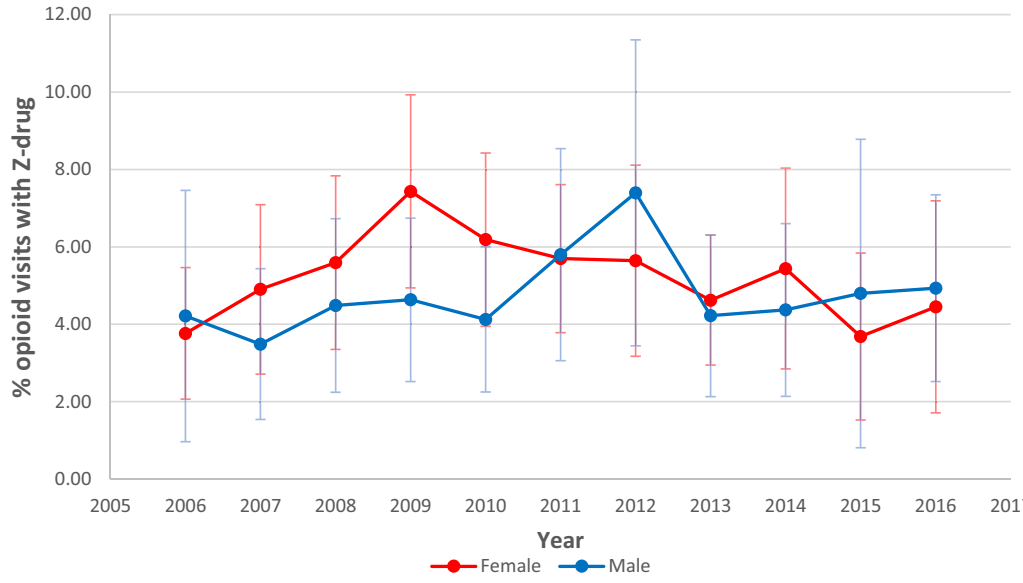

Figure 3. Co-utilization of opioids and Z-drugs stratified by sex, 2006-2016. Error bars indicate 95% CIs.

Table 2
Multivariable logistic regression model results for inclusion of both an opioid prescription and a Z-drug prescription in a single office visit

Characteristic	Opioid + Z-drug, n (% opioid visits)	aOR (95% CI)
Year		
2006–2008	7,793,787 (4.5)	1.0 (REF)
2009–2012	12,922,533 (5.8)	1.26 (0.97–1.65)
2013–2016	7,494,203 (4.4)	0.97 (0.67–1.39)
Women (%)	17,324,123 (5.3)	1.09 (0.86–1.38)
Age, y		
18–34	2,049,034 (2.8)	1.0 (REF)
35–49	7,095,859 (4.9)	1.74 (1.13–2.67)
50–64	13,018,468 (6.9)	2.39 (1.55–3.70)
≥ 65	6,047,161 (3.9)	1.12 (0.65–1.93)
Race		
White only, non-Hispanic	23,016,594 (5.5)	1.61 (1.07–2.45)
Black only, non-Hispanic	2,458,135 (3.6)	1.0 (REF)
Hispanic	1,903,590 (3.5)	1.02 (0.58–1.78)
Other or Multiple	832,204 (3.6)	1.09 (0.51–2.36)
Payer		
Private	12,301,683 (5.2)	1.0 (REF)
Medicare	8,804,336 (5.0)	1.19 (0.89–1.59)
Medicaid or CHIP	4,015,947 (6.0)	1.31 (0.83–2.06)
Worker's comp	600,256[a] (3.8)	0.77 (0.36–1.67)
Self-pay	1,053,254 (3.1)	0.63 (0.41–0.95)
Other[b]	1,435,046 (4.0)	0.84 (0.54–1.30)
Region		
Northeast	3,614,183 (4.4)	1.0 (REF)
Midwest	5,404,090 (4.7)	1.04 (0.68–1.60)
South	11,835,230 (5.1)	1.26 (0.87–1.82)
West	7,357,019 (5.5)	1.40 (0.96–2.05)
Comorbidities		
COPD	1,303,044 (3.3)	0.51 (0.32–0.84)
Depression	8,015,091 (8.3)	1.82 (1.42–2.33)
Hypertension	10,934,976 (5.3)	1.06 (0.86–1.32)
Obesity	3,079,343 (5.0)	0.87 (0.60–1.25)
Osteoporosis	1,629,010 (6.9)	1.40 (0.85–2.30)
Asthma	2,246,924 (5.6)	1.03 (0.67–1.59)
Cancer	3,081,776 (6.2)	1.28 (0.91–1.79)
Patient established at office	25,923,631 (5.2)	1.39 (0.96–2.01)

Abbreviations used: aOR, adjusted odds ratio; CHIP, Children's Health Insurance Program; COPD, chronic obstructive pulmonary disease; NAMCS, National Ambulatory Medical Care Survey; REF, reference.
Note: Z-drugs include zolpidem, eszopiclone, and zaleplon.
[a] Weighted estimate based on <30 raw visits.
[b] Other = no charge, charity, blank, unknown, other.

and, thus, captures a vast population of outpatient opioid and Z-drug users allowing for broad generalizability. Previous studies conducted using the NAMCS, including those by Larochelle et al.[12] and Peckham et al.[13] have not reported specifically on the co-utilization of opioids with Z-drugs; instead, Z-drugs were combined with other classes of sedative medications such as benzodiazepines, barbiturates, and muscle relaxants. The inclusion of trazodone, an alternative sleep medication, in this study's co-utilization analysis provides insight into changing prescribing practices for pain and insomnia medication use over time and how such changes correspond with major regulatory advisories. This expands on results revealed by Peckham et al.,[13] which showed decreases in opioid co-utilization with a benzodiazepine, barbiturate, or hypnotic in older adults from 2012 to 2016.

This study was inherently limited by the lack of information on medication dosages and durations captured by the NAMCS, along with the absence of longitudinal data on prescribing. Additional research employing longitudinal data could reveal the durations of overlapping therapies and subsequent outcomes at the patient level, as well as capture changes in therapy such as dosage adjustments or discontinuation of a medication. Moreover, by restricting this analysis to the first 8 medications listed at each visit, true rates of co-utilization were underestimated as shown by the results of a sensitivity analysis (Appendix 2). These rates were likely also underestimated since the NAMCS does not capture medications prescribed by other providers or those obtained without a prescription.

Conclusion

From 2006 to 2016, co-utilization of opioids and Z-drugs at ambulatory care visits fluctuated in the United States with nonsignificant differences by sex. Major regulatory advisories and policy changes related to opioid and Z-drug prescribing occurred during this period and may have contributed to these varying rates of use. This analysis revealed that a portion of co-utilization visits involved the new initiation of both an opioid and a Z-drug on the same day, a potentially problematic prescribing practice given the noted risks of concomitant use. Pharmacists and other health professionals can play important roles in identifying and preventing instances of opioid and Z-drug co-utilization and educating patients on the associated risks. Additional work is needed to further characterize populations most at risk for co-utilization of opioids and Z-drugs and identify the associated negative consequences.

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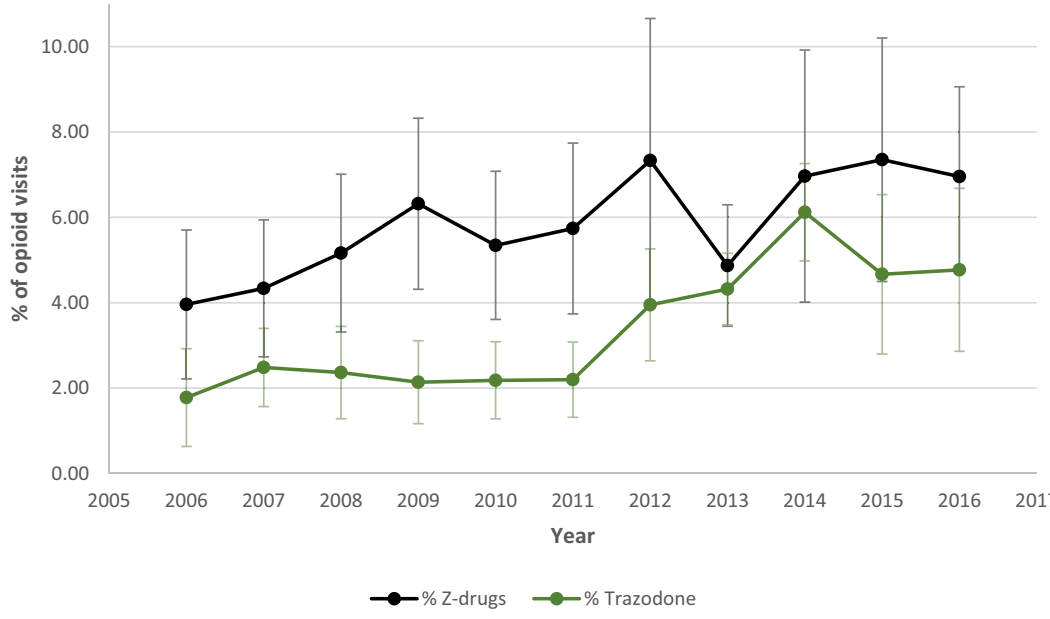
Appendix

Appendix 1
Generic codes and drug entry codes used to identify Z-drugs and trazodone in the MED and DRUGID fields in the NAMCS

Medication class	Medication name	Brand name(s)	Drug Entry Codes (MED)	Generic Codes (DRUGID)
Z-drugs	Eszopiclone	Lunesta	09213, 05033	d05421
	Zaleplon	Sonata	02107, 00039	d04452
	Zolpidem	Ambien, Ambien CR	09614, 94035, 06002, 93347, 12145, 12301, 12346	d00910
Antidepressant	Trazodone	Desyrel, Oleptro	31997, 40520	d00395

Appendix 2

Trends in opioid co-utilization with Z-drugs or trazodone, 2006 – 2016. All medication fields included (not limited to first 8 medication fields). Error bars indicate 95% CIs.



Appendix 3

Weighted counts and percentages of prescriptions indicated as newly initiated and continued therapies among visits including both an opioid and Z-drug (n = 28,210,522)

		Z-DRUG	
		New	Cont'd
Opioid	New	1,968,961 (7.0%)	1,785,246 (6.3%)
	Cont'd	1,397,208 (5.0%)	22,763,607 (80.7%)