Exploratory Research in Clinical and Social Pharmacy 5 (2022) 100130

Contents lists available at ScienceDirect

Exploratory Research in Clinical and Social Pharmacy

journal homepage: www.elsevier.com/locate/rcsop

A descriptive analysis of concomitant opioid and benzodiazepine medication use and associated adverse drug events in United States adults between 2009 and 2018☆

Kathryn K. Marwitz *, Marwa Noureldin

Manchester University College of Pharmacy, Natural & Health Sciences, 10627 Diebold Road, Fort Wayne, IN 46845, United States of America

ARTICLE INFO

Keywords:
Concomitant opioid use
Opioid prescribing
Benzodiazepines
Pharmacovigilance
Medication safety

ABSTRACT

Background: In 2016, the Centers for Disease Control and Prevention (CDC) published guidelines for prescribing opioids for chronic pain in response to the opioid epidemic and recommended avoiding concomitant use of opioid and benzodiazepine medications whenever possible. However, based on a recent report, 16% of overdose deaths involving opioids also involved benzodiazepines.

Objective: The objectives of this study were to examine 1) trends in concomitant opioid and benzodiazepine usage and factors associated with utilization 2) and related adverse event reporting before and after the publication of CDC chronic pain prescribing guidelines.

Methods: This study employed a retrospective data analysis of the National Health and Nutrition Examination Survey (NHANES) and FDA Adverse Event Reporting System (FAERS) databases between 2009 and 2018. Descriptive statistics and logistic regression were used to examine characteristics and temporal trends in people taking or reporting adverse events with opioid, benzodiazepine, and both medications.

Results: Among those taking an opioid medication, 19.7% were also taking a benzodiazepine within the same 30 days. Characteristics for those who reported taking both medications together include being female, non-Hispanic White, being middle aged, and having a lower household income. Concomitant medication use rose between 2009 and 2016 and declined in 2017–2018. Among FAERS reports examined with an opioid suspect medication, 17.9% also included a benzodiazepine suspect medication. Over time, there was an increase in identified FAERS reports involving concomitant opioid and benzodiazepine medications.

Conclusions: Concomitant opioid and benzodiazepine use was detected in a small but notable proportion of NHANES survey participants and FAERS reports between 2009 and 2018. Further research examining causal associations between opioids, benzodiazepines, and identified social risk factors are needed to inform prescribing and to best tailor public health interventions to address physical and mental illness safely and effectively across the population.

1. Introduction

According to the *National Institute on Drug Abuse* in 2019, 16% of overdose deaths involving opioids also involved benzodiazepines.[1] Benzodiazepines, like opioids, cause sedative effects in patients which can contribute to additive respiratory depression risk. Prescribing frequencies of benzodiazepines have increased over the last twenty years in tandem with the rise in opioid misuse.[1] One recent study using the National Health and Nutrition Examination Survey (NHANES) linked to the National Death Index found that the concomitant use of opioids and benzodiazepines may increase long-term mortality risk in those under 65 years compared to those taking selective serotonin reuptake inhibitors (SSRIs).[2] SSRIs were selected as an active comparator in this study because they are used to treat anxiety like benzodiazepines but do not have a known impact on all-cause mortality. Importantly, this comparator helps to reduce confounding by indication further validating the study results.[2] The Centers for Disease Control and Prevention (CDC) guidelines for prescribing opioids for chronic pain in response to the opioid epidemic, which were released in 2016, recommend avoiding concomitant use of opioid and benzodiazepine medications whenever possible and in those who need both medications, recommend additional patient safety measures such as offering naloxone and providing patient education on the symptoms of overdose.[3] Given these updated chronic pain opioid prescribing guidelines and the knowledge of the opioid epidemic and risk for overdose, further information examining the past and

☆ A descriptive analysis of trends in concomitant opioid and benzodiazepine medication use and spontaneously reported adverse drug events in United States adults between 2009 and 2018

* Corresponding author.
E-mail addresses: kkmarwitz@manchester.edu (K.K. Marwitz), mnoureldin@manchester.edu (M. Noureldin).

http://dx.doi.org/10.1016/j.rcsop.2022.100130
Received 3 October 2021; Received in revised form 24 January 2022; Accepted 16 March 2022
Available online xxxx

present use of opioid and benzodiazepine medications concomitantly and factors associated with such use is warranted.

An examination by Veronin and colleagues from 2019 describes the US Food and Drug Administration Adverse Event Reporting System (FAERS) as an important source of adverse event detection for opioid medications.[4] This study found that reports of oxycodone, hydrocodone, and fentanyl accounted for more than half of all opioid adverse event reports.[4] Another examination by McDonald and Srisopa used the FAERS database to identify predictors of serious life-threatening opioid adverse events and found that the risk of taking an opioid and benzodiazepine together with additional sedative medication increased the risk of a serious adverse event by nearly 19 times.[5] These data showcase the utility of examining large, publicly available databases, such as FAERS, for serious and life-threatening overdose reports with opioids and benzodiazepines.

This study has two aims. The first aim is to examine the trends in concomitant opioid and benzodiazepine usage among a nationally representative participant sample between 2009 and 2018. This ten-year timespan offers an in-depth overview of opioid and benzodiazepine utilization within the context of significant changes in prescriber and public awareness of opioid misuse and overuse within the last decade.[1,3] The second aim is to evaluate and describe trends of serious adverse event cases reported to the FAERS during the same timespan for concomitant opioid and benzodiazepine usage with the intent to describe adverse event trends reported with these medications.[6] While the literature currently describes opioid utilization and associated risks with concomitant benzodiazepine use, there is a paucity of evidence comparing opioid and benzodiazepine utilization together with a review of adverse event data.[1,2,4,5] While prescription medication utilization can inform on prescribing patterns, reports of adverse events can inform on the patient experience. Combining knowledge of utilization and adverse event reports provides a broader landscape of the prescription journey from the prescriber's recommendation through the patient's treatment regimen.

2. Materials and methods

2.1. Datasets

2.1.1. NHANES

For the first aim, a retrospective examination of NHANES was employed.[7] NHANES is a collection of studies examining the health and nutrition status of adults and children within the U.S.[7] Combining physical examinations and participant interviews, NHANES is a nationally representative sample of about 5000 individuals per year. NHANES collects information pertaining to the participants' demographic, socioeconomic, dietary, and health characteristics through patient interviews and medical, dental, physiological, and lab values through patient examination. Methods for NHANES participant selection are standardized and described thoroughly by the CDC National Center for Health Statistics (NCHS).[7] Prescription drug information, including drug generic name, duration, and indication, are collected during the participant interview and prescription medications are verified by the interviewer through examination of medication bottles.

2.1.2. FAERS

For the second aim, an examination of adverse event reporting trends with concomitant use of opioids and benzodiazepines was employed using FAERS. FAERS is the post-marketing surveillance program through the FDA tracking spontaneous adverse event reporting for marketed drug and biologic products.[6] Through codified federal regulations, manufacturers are required to submit adverse event reports to FAERS. FAERS also collects adverse event reports from healthcare providers, consumers, and the published literature.[6] Adverse event reports follow the International Conference on Harmonisation guidance and reports are also coded using the Medical Dictionary for Regulatory Activities (MedDRA).[6] De-identified FAERS data are made available to the general public through the FAERS dashboard and FAERS data files.[6]

2.2. Data extraction and Inclusion Criteria

This study was deemed exempt after Institutional Review Board review. NHANES data files between 2009 and 2018 were obtained from the NCHS website.[7] All subjects who answered prescription drug questionnaire with a drug name on NHANES between 2009 and 2018 were included for analysis. Individuals taking the following medications were designated as affirmative for opioid use: *Buprenorphine, Butorphanol, Codeine, Fentanyl, Hydrocodone, Hydromorphone, Levorphanol, Meperidine, Methadone, Morphine, Nalbuphine, Oxycodone, Oxymorphone, Pentazocine, Tramadol, and Tapentadol.* Those who take the following medications were designated as affirmative for benzodiazepine use: *Alprazolam, Chlordiazepoxide, Clonazepam, Clorazepate, Diazepam, Estazolam, Flurazepam, Lorazepam, Midazolam, Oxazepam, Quazepam, Temazepam, and Triazolam.* Those taking at least one opioid and one benzodiazepine were affirmed as a person who used both medications within the past 30 days of the participant interview. The following health information interview information for survey participants was extracted: medication name(s), gender, race and ethnicity, education level, marital status, household income, and age were extracted. Medication use duration was not analyzed for this study because the variable was self-reported and not reliably available.

Identical criteria used to determine opioid and benzodiazepine usage in NHANES medication usage by opioid and benzodiazepine classification were used to classify FAERS reports. FAERS case data for all medications between 2009 and 2018 reporting the following MedDRA preferred terms were extracted from the FAERS public dashboard: *accidental poisoning, accidental overdose, confusional state, death, inappropriate schedule of product administration, intentional product misuse, intentional overdose, off label use, overdose, poisoning, poisoning deliberate, respiratory arrest, respiratory depression, somnolence, and toxicity to various agents* Case reports that did not report one of these MedDRA preferred terms were not included in the analysis. These MedDRA preferred terms were selected based on known adverse drug reactions with concomitant opioid and benzodiazepine usage and primary author's expertise of pharmacovigilance reporting. All case data included in the FAERS public dashboard for relevant case reports including suspect medication, concomitant medications, patient age, sex, adverse event outcome, and case seriousness were extracted.

2.3. Analysis

2.3.1. NHANES

NHANES surveys for five two-year cycles (2009–2018) were combined. The data were weighted using the interview weights calculated for the 10-year interval which help account for differential probabilities of survey selection and response.[8] Statistical reliability was determined per the NHANES analytic guidance documents available using sample size, relative, and absolute confidence interval widths for proportional measurements and estimated and standard error calculations for regression models. NHANES recommends avoiding suppressing statistically unreliable measures as they still may have clinical importance.[9–12] Any values not meeting statistical reliability were marked in the tables below. Appendix A contains unweighted data and measures used to determine statistical reliability.

Descriptive statistics measuring total counts, percentages, and means were calculated for demographic variables. Survey-weighted bivariate logistic regression was performed to determine demographic and social factors impacting the likelihood of taking an opioid with a benzodiazepine. Survey-weighted multiple variable logistic regression was performed to determine odds of taking an opioid with a benzodiazepine based on relevant demographic factors. Statistical significance was determined at an alpha of 0.05. All analysis were performed in Stata Version 14.2 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

2.3.2. FAERS

Relevant case report data between 2009 and 2018 were combined for analysis. Descriptive statistics including percentages, proportions, and

total counts were used to describe adverse event case reporting trends over time and by age, sex, and case seriousness as determined by US Food and Drug Administration (USA FDA). Serious case reports are cases that result in death or cases where the reaction is life-threatening, requires hospitalizations, prolongs current hospitalization, results in persistent or significant disability, contributes to a congenital birth anomaly, or is otherwise deemed medically important.[13] All analysis were performed in Stata Version 14.2 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP) and Microsoft Excel (Microsoft Office Professional Plus 2016).

3. Results

3.1. NHANES

There were 49,693 interview entries included in this study analysis spanning 2009–2018. Of these 49,693 study participants, 1902 (4.7%) reported taking an opioid medication in the past 30 days and 1186 (3.4%) reported taking a benzodiazepine in the past 30 days. Of those taking an opioid medication in the last 30 days, 347 (19.7%) were also taking a benzodiazepine. Table 1 describes the weighted demographic characteristics for the study participants.

Trends in opioid, benzodiazepine and opioid with benzodiazepine use have changed over time. In 2009–2010 and 2011–2012, 15.6% and 15.9% of persons on an opioid medication were also on a benzodiazepine medication, respectively. In 2013–2014, that proportion went up to 22.6% of opioid medication users. In 2015–2016, 25.6% of persons on an opioid medication were also on a benzodiazepine. The odds of being on a benzodiazepine when also on an opioid medication were highest in 2013–2014 (OR = 1.78, 95% CI 1.11–2.86, *p*-value = 0.016) and 2015–2016 (OR = 1.66, 95% CI 1.01–2.72, p-value = 0.04) compared to the 2017–2018 timeframe where only 13.8% of opioid users were also on a benzodiazepine.

Based on the results of the bivariate logistic regression (Appendix Table A.1), a multivariable logistic regression was conducted and results demonstrated that the odds of being a female and on both an opioid and benzodiazepine together in the last 30 days compared to males was 1.42 (95% CI 1.03–1.94). Participants aged 30 to 49 years old, 50 to 64 years old, and 65–79 years old had an increased likelihood of being on an opioid and benzodiazepine together in the last 30 days compared to those aged 18 to 29 years (OR = 2.87 95% CI (1.26–6.52); OR = 5.83 95% CI (2.54–13.38); OR = 3.62 95% CI (1.40–9.36), respectively). Survey participants who were taking both opioid and benzodiazepine medications were majority non-Hispanic White (83.5%). Individuals who identify as Black, Mexican American, Multi-racial, and other Hispanic were less likely to be on concomitant opioid and benzodiazepines compared to non-Hispanic White participants (OR = 0.28 95% CI (0.18–0.42); OR = 0.21 95% CI (0.12–0.36); OR = 0.52 95% CI (0.29–0.94); OR = 0.25 95% CI (0.14–0.42)). Participants who were most highly educated were least likely to be on concomitant opioid and benzodiazepine medication compared those who completed high school or a General Education Development (GED) test (OR = 0.44, 95% CI 0.25–0.77). Participants with households making less than $20,000 and $20,000–$44,999 annually were more likely to be on the medication combination (OR = 3.71, 95% CI (1.91–7.23); OR = 2.14, 95% CI (1.15–4.00)). Table 2 describes medication use by age, race, ethnicity, income, marital status, and educational level characteristics. Appendix Table A.2 describes the weighted proportions data.

3.2. FAERS

A total of 1,101,300 adverse event case reports were extracted from FAERS using the fifteen MedDRA preferred terms identified above during 2009–2018. After removing case reports that were retrieved twice because they contained more than one of the identified preferred terms (n = 82,639) and cases where report year was miscoded (n = 4087),

Table 1
Weighted demographic characteristics of NHANES health interview participants from 2009 to 2018.

Characteristic	Count (n = 49,693)	Weighted Percentage	95% CI
Medication			
Neither	46,952	92.8%	92.5–93.2%
Opioid	1902	4.7%	4.4–5.0%
BZD	1186	3.4%	3.1–3.6%
Percent of opioid users taking concomitant BZD[a]	347	19.7%	17.3–22.4%
Gender			
Female	25,160	51.1%	50.5–51.6%
Male	24,533	48.9%	48.2–49.5%
Average age	37.6 years		37.3–37.8%
Race and ethnicity			
Non-Hispanic White	17,283	61.9%	61.3–62.4%
Non-Hispanic Black	11,151	12.1%	11.8–12.3%
Mexican American	8757	10.5%	10.2–10.8%
Other/Multi-Racial	7205	8.9%	8.7–9.2%
Other Hispanic	5297	6.6%	6.4–6.8%
Education			
<9th grade	2943	3.9%	3.7–4.1%
9–11th grade	3892	7.4%	7.1–7.7%
HS/GED	6459	17.0%	16.1–17.1%
Some college	8639	23.3%	22.7–23.7%
College graduate	6857	22.3%	21.7–22.9%
Missing	20,858	26.4%	26.0–26.9%
Household Income			
<$20,000	9634	13.3%	12.9–13.6%
$20–44,999	13,918	23.4%	22.9–23.9%
$45–54,999	3565	7.6%	7.2–7.9%
$55–64,999	2733	6.2%	5.8–6.5%
$65–74,999	2148	5.2%	4.9–5.6%
$75–99,999	4306	11.2%	10.7–11.6%
$100,000+	7931	24.0%	23.4–24.6%
Missing/Unknown	5458	9.1%	8.8–9.5%

BZD = benzodiazepine; [a] = calculated as the proportion of survey participants on BZD and opioids divided by the proportion of survey participants on opioids.

Table 2
Weighted multiple variable logistic regression examining demographic and social factors' impact on concurrent opioid and benzodiazepine (BZD) use.

Characteristic		OR	SE	95% CI
Age	18–29 years	1		
	30–49 years	2.87	1.20	1.26–6.52
	50–64 years	5.83	2.47	2.54–13.38
	65–79 years	3.62	1.75	1.40–9.36
	>79 years	2.74	1.42	0.99–7.54
Gender	Male	1		
	Female	1.42	0.23	1.03-1.94
Race and ethnicity	White	1		
	Black	0.28	0.06	0.18–0.42
	Mexican	0.21	0.06	0.12–0.36
	Other/MR	0.52	0.16	0.29–0.94
	Other Hispanic	0.25	0.07	0.14–0.42
Education	<9th grade	0.80	0.24	0.45–1.42
	9–11th grade	1.37	0.32	0.87–2.16
	HS/GED	1		
	Some college	1.03	0.21	0.69–1.54
	College graduate	0.44	0.12	0.25–0.77
Marital Status	Married	0.92	0.29	0.49–1.74
	Widowed	1.12	0.48	0.49–2.59
	Divorced	1.38	0.47	0.70–2.70
	Separated	2.00	0.93	0.80–5.01
	LWP	1.181	0.45	0.56–2.49
	Never Married	1		
Household Income	<$20,000	3.71	1.26	1.91–7.23
	$20–44,999	2.14	0.68	1.15–4.00
	$45–54,999	2.00	0.73	0.97–4.10
	$55–64,999	1.01	0.50	0.39–2.64
	$65–74,999	1.74	0.85	0.68–4.51
	$75–99,999	0.791	0.36	0.33–1.92
	$100,000+	1		

1,014,574 total case reports were included for analysis. Among these reports, 81,972 (8.1%) cases reported at least one opioid medication as a suspect medication for the reported adverse event(s). In addition, 36,645 (3.6%) cases reported use of benzodiazepine as a suspect medication. Of the FAERS reports reporting opioid as a suspect product, 17.9% also reported a benzodiazepine. The average age reported for all adverse event case reports was 56.7 years old with over 40% (n = 414,635) of reported age classified as unknown. In comparison, the average age of individuals in case reports with concomitant use of opioids and benzodiazepines was 42.7 years old. While 71% all adverse event cases were deemed by US FDA to be serious, nearly all (99.1%) of concomitant use opioid and benzodiazepines case reports were deemed serious. FAERS also provides information about the source of adverse event case reports. Over 50% of all reported cases came from healthcare providers while 46% of cases were reported by consumers. In comparison, 88.9% of concomitant use opioid and benzodiazepine reports were reported by healthcare providers and only 8.2% of reports were reported by consumers.

In 2009, only 4.4% of all case reports with the previously mentioned preferred terms involved an opioid medication concomitantly with a benzodiazepine. By 2018, that percentage tripled to 12.7% of reported cases with these preferred terms. Table 3 describes these trends across overall, opioid, benzodiazepine, and concomitant opioid with benzodiazepine case reports.

4. Discussion

Among NHANES survey participants, concomitant use was rising between 2009 and 2016. After 2016, the proportion of those taking an opioid and benzodiazepine medication together declined sharply from 25.6% of opioid users to 13.7%. This sharp decline is potentially attributed to several policy and regulatory decisions and changes in knowledge, behaviors, and attitudes around prescribing and taking opioid medications. In 2016, CDC published a morbidity and mortality weekly report (MMWR) with guidelines for prescribing opioids for chronic pain.[3] This set of guidelines recommended against the use of opioid and benzodiazepine concomitantly, when possible. These guidelines were released during an environment where policymakers, clinicians, and the public were largely focused on the opioid epidemic with added emphasis on judicious prescribing.[14–16] The US FDA also added a boxed warning to the opioid class of medications regarding the risk of overdose when using opioids and benzodiazepine concurrently[17]. One study using a longitudinal patient prescription database containing retail pharmacy claims data examined the impact of this regulatory change and found a statistically significant decrease in concomitant opioid and benzodiazepine prescribing after US FDA required this medication labeling change.[18] The greatest decreases in concomitant prescribing were seen among women and among those 50–65 years old.[18]

Moreover, there was a notable shift in prescriber, pharmacy, and the public's awareness of the opioid epidemic. One recent study describes reductions in opioid prescribing by emergency medicine, surgery, and dentistry specialties attributed to the use of state prescription drug monitoring programs (PDMPs), pain clinic licensing laws, and prescription insurance reimbursement changes.[19] The American Medical Association (AMA) released a statement in 2015 regarding the opioid crisis urging prescribers to utilize PDMPs and enhance training for opioid prescribing among other initiatives.[20] PDMPs do have limitations, however, because

Table 3
Comparison of FAERS case reports with opioid, benzodiazepine (BZD), both, and neither as suspect medications between 2009 and 2018 for identified preferred terms*.

BZD = benzodiazepine; Other/MR = Other race/multi-racial; HS = high school; GED = General Educational Development test; LWP = living with partner	Overall	Opioid	BZD	Opioid w/ BZD
Number of reports[a]	1,014,574	81,972 (8.1%)	36,645 (3.6%)	14,686 (1.5%)
Average age (years)	56.7 (+/− 0.03)	47.4 (±0.1)	45.0 (±0.1)	42.7 (+/− 0.1)
% missing	40%	46.6%	15.2%	9.8%
Sex				
Female	500,029 (49.3%)	27,492 (33.5%)	18,509 (50.5%)	6722 (45.8%)
Male	383,062 (37.8%)	25,752 (31.4%)	15,170 (41.4%)	7079 (48.2%)
Missing	131,483 (13.0%)	28,728 (35.1%)	2966 (8.1%)	885 (6.0%)
Case seriousness				
Serious	720,031 (71.0%)	74,626 (91.0%)	35,208 (96.1%)	14,461 (99.1%)
Non-serious	294.543 (29.0%)	7346 (9.0%)	1437 (3.9%)	125 (0.9%)
Case reporter				
HCP	530,694 (52.3%)	44,198 (53.9%)	31,024 (84.7%)	13,059 (88.9%)
Consumer	462,960 (45.6%)	36,370 (44.4%)	4625 (12.6%)	1203 (8.2%)
Unknown	20,919 (2.1%)	1404 (1.7%)	996 (2.7%)	424 (2.9%)
Five most frequently reported preferred terms	Death	Toxicity to various agents	Toxicity to various agents	Toxicity to various agents
	Off label use	Death	Completed suicide	Drug abuse
	Somnolence	Overdose	Drug abuse	Death
	Toxicity to various agents	Drug abuse	Death	Completed suicide
	Inappropriate schedule of product administration	Somnolence	Overdose	Respiratory arrest
Case count per year				
2009	31,818 (3.1%)	3597 (4.4%)	1494 (4.1%)	587 (4.4%)
2010	46,439 (4.6%)	3826 (4.7%)	2271 (6.2%)	1050 (7.2%)
2011	52,425 (5.2%)	4328 (5.3%)	2505 (6.8%)	1087 (7.4%)
2012	78,816 (7.8%)	5072 (6.2%)	2938 (8.0%)	1214 (8.3%)
2013	79,158 (7.8%)	7134 (8.7%)	4348 (11.9%)	2057 (14.0%)
2014	93,391 (9.2%)	7093 (8.7%)	4812 (13.1%)	2264 (15.4%)
2015	132,599 (13.1%)	7206 (8.8%)	4200 (11.5%)	1757 (12.0%)
2016	138,215 (13.6%)	5565 (6.8%)	3432 (9.4%)	1129 (7.7%)
2017	172,524 (17.0%)	9.016 (11%)	5149 (14.1%)	1670 (11.4%)
2018	189,189 (18.7%)	29,135 (35.5%)	5496 (15.0%)	1871 (12.7%)

HCP = Health care provider.

* Preferred terms include: accidental poisoning, accidental overdose, confusional state, death, inappropriate schedule of product administration, intentional product misuse, intentional overdose, off label use, overdose, poisoning, poisoning deliberate, respiratory arrest, respiratory depression, somnolence, and toxicity to various agents; a: divided each number by 1,014,574 to obtain percentages of total case.

not every required medication is always reported. In 2016, Massachusetts was the first state to limit, by law, the prescribing of first-time opioid prescriptions to seven days.[21] Several other states have followed suit. Pharmacies nationwide have also responded to the opioid crisis. Shafer and colleagues describe one pharmacy chain's initiatives to improve access to naloxone and safe medication disposal sites along with providing patient education to reduce risk of opioid overdoses.[22] With reductions in opioid prescribing, increased knowledge about opioid-related risks, and policy and regulatory changes at the national, state, and local levels that influenced the availability of opioids, concomitant opioid and benzodiazepine use could have also been impacted.

In this analysis, concomitant opioid and benzodiazepine use was detected in a small but noteworthy proportion of NHANES survey participants between 2009 and 2018. Among those taking an opioid medication, 19.7% were also taking a benzodiazepine within the same 30 days. Previous published literature has found varying results.[23–24] Hwang and colleagues examined outpatient prescription utilization data between 2002 and 2014 and found the percentage of patients prescribed a benzodiazepine when already on an opioid medication increased from 6.8% to 9.6%.[23] This study also found in over half of concomitant prescriptions, both medications were written by the same prescriber.[23] Hwang and colleagues only examined commercially insured patients whereas this current study examined a nationally representative sample across the US population. Another study by Simon and colleagues from 2018 examined 2000 outpatient psychiatrist clinic visits between January and April 2018.[24] They used the state prescription drug monitoring program to identify which patients from their study filled an opioid or benzodiazepine in the last 12 months and found 353 patients who met this criteria.[24] Of the 324 patients who filled an opioid medication, 49.4% also filled a benzodiazepine medication concurrently.[24] This study found higher concomitant utilization of opioids and benzodiazepine medications compared to the current analysis which may be attributed to the needs and relevant indications of the psychiatric practice examined.

Characteristics for those who reported taking both opioid and benzodiazepine medications from this study include identifying as female, as non-Hispanic White, being middle aged, and having a lower household income. Likely, these demographic characteristics represent underlying social factors influencing healthcare access and medication use patterns among the US population. Prior data demonstrate that counties with higher prescribing of opioid medications are ones with a greater number of White residents, a greater number of residents who are uninsured and unemployed, and a greater number of residents who have common chronic health conditions such as diabetes and arthritis.[25–26] Benzodiazepine use is also commonly seen among women, those of middle and older age, and those who are uninsured or who self-pay for healthcare.[27] Studies examining demographic characteristics for concomitant use of opioids and benzodiazepines are limited, however, small studies indicate women, those of middle and older age, or those who take chronic opioid medications are more likely to be on both medication classes together.[23–24]

The association between concomitant opioid and benzodiazepine use and lower income and education may be partially explained through the disproportionate increase in mental health disorders among those of lower socioeconomic status.[28] Those of lower socioeconomic status often face greater physical, social, and environmental stress leading to poor physical and mental health which may increase the likelihood for being prescribed medications to address these health conditions.[28] However, those of lower socioeconomic status also experience challenges in accessing the U.S. healthcare system.[29] Concurrently, some evidence supports that they are at a higher risk of receiving substandard care, including the use of contraindicated medications.[29] Further understanding the relationship between income, education, and concomitant opioid and benzodiazepine utilization remains important to improve the safe use of these medications.

Adverse event reporting in FAERS over time have seen year-by-year increases due to greater electronic reporting mechanisms, greater number of US FDA-approved medications per year, and prioritization on pharmacovigilance activities.[30–31] However, there is still significant underreporting issues in FAERS as a pharmacovigilance database. Adverse event reporting in FAERS for opioids, benzodiazepines, and concomitant opioid and benzodiazepines have followed a dissimilar pattern to that of NHANES data. Adverse event reporting trended upwards for all three groups between 2009 and 2014. All three groups trended downward in reporting volume after 2014 and another increase in and after 2016. Increases in adverse event reporting for opioids, benzodiazepine, and opioid and benzodiazepine cases between 2012 and 2014 and 2016–2018 were possibly due to increased awareness of risks and increased adverse event frequency associated with increased utilization of opioids, benzodiazepines, and both medications together.[32–33] In addition, US FDA scans and enters relevant published literature such as case reports involving a medication and an adverse event into FAERS.[6] Published literature such as the American Association of Poison Control Centers Annual report have seen increases in reports for analgesics, sedatives, and hypnotic medications over the years, which could have played a role in the increased report volume seen in FAERS.[34–35] This seemingly dissimilar pattern to the utilization rates and notable increase in opioid adverse reports between 2017 and 2018 is possibly linked to litigation activities regarding the opioid epidemic and opioid medication manufacturers in addition to national recognition of opioid risks and consequences.[36–37]

5. Limitations

There are several limitations to this study. NHANES data are observational in nature and are obtained through participant interviews. As such, participants may not accurately recall their prescribed medications which can lead to non-differential misclassification of medication utilization. However, NHANES staff are trained to obtain accurate medication histories and aim to verify all prescription medications by reviewing participant medication bottles or calling the participant's pharmacy. In addition, NHANES data do not reliably contain dosage information. Recognizing that concomitant opioid and benzodiazepine medication risk changes with increasing doses, this study was not able to discern risk changes based on this important risk factor. These data were analyzed through 2018 and not into more recent years because the 2019–2020 NHANES cycle was interrupted due to Coronavirus Disease 2019 pandemic.[38] The NHANES data available as a result of the disruption have been combined into a unique pre-pandemic file that is nationally representative.[38] However, this study aimed to examine trends longitudinally to capture relevant policy and regulatory changes and the NHANES pre-pandemic data file was alone insufficient to capture this.

The FAERS data also have limitations. FAERS data are collected as spontaneous reported adverse events and do not describe incidence and prevalence of reported adverse events. FAERS data are observational in nature and no causal association between the reported adverse event and reported medication can be drawn. However, adverse event reporting provides a subset of adverse event trends that can be used to generate hypotheses for future studies. Data contained in FAERS may also be duplicate and this analysis was not able to account for duplicate case reports. Should duplicates be contained in this analysis, their impact is likely to be minimal. It is also possible that additional adverse event reports including opioids and benzodiazepines together and separate may not have been captured in this study due to the selection of preferred terms used to mine the data. However, the preferred terms selected describe known adverse events associated with concomitant opioid and benzodiazepine use which provides a reliable measure of anticipated patient safety risks that could be captured within FAERS. This analysis sought to describe these known safety risks and compare case report trends with medication utilization over time. Lastly, this study did not examine the impact of non-benzodiazepine hypnotic medications and gabapentinoids which have also shown an increased risk of overdose when used with opioids.[39] Additional research could examine utilization and adverse event trends with opioids, benzodiazepines, non-benzodiazepine hypnotic, and gabapentinoid medications.

6. Conclusions

This study sought to examine medication utilization and adverse event reporting trends in persons taking concomitant opioid and benzodiazepine medications. By examining the 2009–2018 NHANES survey data, this study demonstrated trends in concomitant opioid and benzodiazepine use steadily increased until 2016. Several regulatory, policy, and guidelines were developed and released around this time seeking to address the opioid epidemic. Those more likely to be on that medication combination included females, middle aged and older adults, those from lower income households, and those identifying as White. These associations between concomitant opioid and benzodiazepine usage may represent an impact of underlying social factors, including healthcare access, which may be of interest for providers caring for patients with chronic physical and mental illness. The FAERS data provide descriptive information regarding adverse events reported with opioid and benzodiazepine medication. While these data have several limitations, they also provide further evidence of the impact of regulatory and policy decision-making on adverse event reporting.

The results of this study demonstrate some ways current policies, regulatory changes, and guidelines have impacted practice as well as highlighted where future changes may be needed. Despite available evidence describing the risks, concomitant use of opioids and benzodiazepines persist. Further research examining causal associations between opioids, benzodiazepines, and identified social risk factors are needed to inform prescribing and to best tailor public health and policy interventions to address physical and mental illness safely and effectively across the population.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None.

Acknowledgements

The authors would like to thank Angela Jiang who helped with initial data preparation and review in the early stages of this project.

Appendix

Table A.1
Weighted bivariate variable logistic regression examining demographic and social factors' impact on concurrent opioid and benzodiazepine (BZD) use.

Characteristic		Odds Ratio comparing likelihood of opioid with BZD		
		OR	SE	95% CI
Age	<18 years	1		
	18–29 years	11.13	6.15	3.7–33.5
	30–49 years	30.48	18.20	9.2–110.1
	50–64 years	71.81	41.68	22.6–228.1
	65–79 years	57.22	33.54	17.8–183.9
	>79 years	53.3	32.60	15.8–180.1
Gender	Male	1		
	Female	1.73	0.22	1.33–2.32
Race and ethnicity	White	2.3	0.67	1.29–4.12
	Black	0.82	0.25	0.45–1.49
	Mexican	0.52	0.17	0.27–0.99
	Other/MR	1		
	Other Hispanic	0.55	0.20	0.26–1.14
Education	<9th grade	0.65	0.20	0.35–1.18
	9-11th grade	1.39	0.34	0.86–2.24
	HS/GED	1		
	Some college	0.99	0.16	0.72–1.36
	College grad	0.32	0.08	0.19–0.52
Marital Status	Married	1.43	0.41	0.81–2.54
	Widowed	4.04	1.29	2.13–7.63
	Divorced	3.87	1.16	2.13–7.01
	Separated	4.03	1.74	1.71–9.52
	NM	1		
	LWP	1.42	0.53	0.67–2.99
Household Income	<$20,000	4.23	1.29	2.31–7.75
	$20–44,999	2.42	0.71	1.35–4.34
	$45–54,999	2.22	0.89	1.01–4.92
	$55–64,999	1.16	0.41	0.57–2.35
	$65–74,999	2.01	0.92	0.80–5.03
	$75–99,999	0.80	0.40	0.29–2.16
	$100,000 +	1		

BZD = benzodiazepine; Other/MR = Other race/multi-racial; HS = high-school; GED = General Educational Development test; LWP = living with partner; NM = never married.

Table A.2
Weighted comparison of opioid, benzodiazepine (BZD), opioid with BZD with confidence intervals by demographic and social factors.

		Opioid		BZD		Opioid with BZD	
		Percent	95% CI	Percent	95% CI	Percent	95% CI
Age	<18 years	2.0%	1.4–2.9%	1.3%+	0.7–2.2%	0.7%+	0.2–2.3%
	18–29 years	9.9%	8.2–11.9%	9.6%	7.5–12.2%	5.6%+	2.9–10.6%
	30–49 years	26.4%	23.3–29.8%	27.9%	24.4–31.7%	23.7%	18.0–30.4%
	50–64 years	38.3%	34.2–42.6%	35.2%	30.9–39.8%	45.8%	38.2–53.6%
	65–79 years	18.1%	15.6–20.8%	19.0%	16.3–21.9%	18.6%	13.9–24.5%
	>79 years	5.3%	4.3–6.5%	7.0%	5.7–8.6%	5.5%+	3.5–8.7%
Gender	Male	43.1%	40.0–46.2%	37.7%	33.9–41.5%	35.7%	29.2–42.7%
	Female	56.9%	53.8–60.0%	62.3%	58.5–66.1%	64.3%	57.3–70.1%
Race and ethnicity	White	73.3%	71.1–75.5%	83.6%	81.5–85.5%	83.5%	79.4–87.0%
	Black	11.4%	10.2–12.7%	4.9%	4.0–5.9%	5.9%+	4.2–8.2%
	Mexican	5.7%	4.8–6.7%	3.7%	3.0–4.7%	3.2%+	2.1–4.9%
	Other/MR	6.0%	4.8–7.5%	4.5%	3.4–5.9%	5.3%+	3.2–8.5%
	Other Hispanic	3.5%	2.9–4.3%	3.3%	2.7–4.2%	2.1%+	1.3–3.5%
Education	<9th grade	3.9%	3.3–4.7%	4.7%	3.8–6.0%	4.2%+	2.6–6.6%
	9-11th grade	14.4%	12.6–16.4%	12.1%	10.2–14.5%	16.8%	12.5–22.2%
	HS/GED	27.8%	25.0–30.7%	23.9%	20.8–27.1%	27.6%	21.6–34.5%
	Some college	36.0%	33.0–39.1%	34.0%	30.4–37.7%	38.5%	31.7–45.7%
	College grad	14.7%	12.5–17.3%	23.4%	20.0–27.3%	12.0%	8.1–17.4%
Marital Status	Married	49.8%	46.8–53.0%	47.3%	43.5–51.2%	42.6%	35.8–49.7%
	Widowed	9.0%	7.6–10.7%	10.6%	8.6–13.0%	12.8%	8.8–18.3%
	Divorced	15.1%	13.1–17.4%	16.1%	13.6–18.9%	21.6%	16.3–28.0%
	Separated	3.7%	2.7–5.0%	4.4%	3.1–6.2%	5.3%+	2.8–9.7%
	NM	12.1%	10.3–14.2%	14.2%	11.7–17.2%	10.4%	6.5–16.1%
	LWP	7.0%	5.6–8.7%	5.6%	4.2–7.5%	6.5%+	4.0–10.4%
Household Income	<$20,000	21.7%	19.7–24.0%	18.9%	16.5–21.4%	28.6%	23.1–34.8%
	$20–44,999	28.2%	25.6–31.1%	27.9%	24.9–31.4%	29.1%	23.1–35.9%
	$45–54,999	9.0%	7.2–11.1%	7.6%	5.8–9.9%	8.6%	5.3–13.7%
	$55–64,999	5.8%	4.5–7.4%	5.0%	3.5–7.1%	3.7%+	1.7–7.9%
	$65–74,999	5.7%	4.2–7.6%	6.5%	4.7–9.0%	5.4%+	2.5–11.3%
	$75–99,999	8.2%	6.5–10.3%	7.1%	5.0–9.9%	4.6%+	2.2–9.2%
	$100,000+	14.4%	12.0–17.2%	19.9%	16.1–22.7%	12.4%	8.1–18.6%

BZD = benzodiazepine; Other/MR = other race/multi-racial; HS/GED = high-school/General Education Development test; LWP = living with partner; NM = never married.

+ Does not meet NHANES statistical reliability standards, take caution with interpretation of results.

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