Hospitalization and Combined Use of Opioids, Benzodiazepines, and Muscle Relaxants in the United States

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Abstract

Introduction: Concurrent opioid and benzodiazepine use ("double-threat") and double-threat and muscle relaxant use ("triple-threat") are postulated to increase morbidity versus opioids alone. Study objectives were to measure association between double- and triple-threat exposure and hospitalizations in a validated, nationally representative database of the United States. **Methods:** A retrospective cohort study was conducted using the 2013 and 2014 Medical Expenditure Panel Survey (MEPS) longitudinal dataset and affiliated Prescribed Medicines Files. Association between 2013 and 2014 double- and triple-threat exposures and outcome of hospitalizations compared to nonusers, opioid users, and all combinations were assessed via logistic regression. The cohort surveyed in MEPS has been weighted to be reflective of the actual US population in the years 2013 and 2014. Logistic regression applying the subject-level MEPS survey weights was performed to measure association via odds ratios (ORs) of medication exposures with the outcome of all-cause hospitalization. Study subjects were categorized into exposure groups as nonusers (nonuse of opioids, benzodiazepines, or muscle relaxants), opioid users, benzodiazepine users, muscle relaxant users, "double-threat" users, and "triple-threat" users. Analyses were conducted using RStudio® 1.1.5 (Boston, MA) with α level = 0.05 for all comparisons. **Results:** Opioids, benzodiazepines, and muscle relaxants were used in 11.9% (38.4 million), 4.2% (13.5 million), and 3.4% (10.9 million) lives of the United States in 2013, respectively. Double-threat prevalence rose from 1.6% to 1.9% from 2013 to 2014. Triple-threat prevalence remained unchanged at 0.53%. Compared to nonusers, triple-threat patients increased hospitalization probability with ORs of 8.52 (95% confidence interval [CI]: 8.50-8.55) in 2013, 5.06 (95% CI: 5.04-5.08) in 2014, and 4.61 (95% CI: 4.59-4.63) in the 2013-2014 longitudinal analysis. Compared to nonusers, double-threat patients increased hospitalization probability with ORs of 5.71 (95% CI: 5.69-5.72) in 2013, 11.47 (95% CI: 11.44-11.49) in 2014, and 5.59 (95% CI: 5.57-5.60) in the longitudinal analysis. **Conclusion:** Concurrent opioid and benzodiazepine use and opioid, benzodiazepine, and muscle relaxant use were associated with increased hospitalization likelihood. Amplified efforts in surveillance, prescribing, monitoring, and deprescribing for concurrent opioid, benzodiazepine, and muscle relaxant use are needed to reduce this public health concern.

Keywords

analgesics, drug/medical use evaluation, pain management, outcomes research

Introduction

On average, 130 Americans die each day due to overdose of an opioid.[1] From 1999 to 2017, overdoses of legal and illicit opioids led to more than 400 000 deaths in the United States.[2] The rise in deaths due to overdoses has been correlated with the recent declines in life expectancy in the United States over the past 3 years with two-thirds of these drug overdose deaths caused by opioids.[3,4] Beyond loss of life, the opioid epidemic has also forced increased spending on medical care for patients with opioid use disorder (OUD) and translated to a loss in worker productivity. The social cost of the opioid epidemic in 2015 was estimated to be US$504 billion by the White House Council of Economic Advisors, and efforts to stifle criminal activity related to opioid abuse are absorbing more money and manpower.[5,6] Opioid use alone has exacted a deadly societal toll, but a related trend that demands attention is the rise of co-prescribing of benzodiazepines and muscle relaxants with opioids. The percentage of opioid users also consuming benzodiazepines rose from 9% in 2001

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to 17% in 2013.[7] An analysis between 2001 and 2010 found benzodiazepines were co-prescribed with opioids in 8.1% of acute pain visits and 15.5% of chronic pain visits with no evidence of decreased co-prescribing during the analysis period.[8] Benzodiazepines increase the level of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the brain resulting in sedation, respiratory depression, and cognitive impairment.[9] Muscle relaxants function at a different binding domain of the GABA receptor, but similarly generate the neuromuscular suppressive effects of benzodiazepines.[10] The combination of benzodiazepines and/or muscle relaxants potentiates the respiratory depression attributable to opioids at the medullary respiratory centers of the brain increasing lethal risk. Combinations of these agents also synergize the euphoria of opioids via enhanced agonism of the μ_1-opioid receptor and possibly by potentiation of the dopaminergic activity of the opioids.[11]

The goal of this study was to use US Department of Health & Human Services (HHS) Medical Expenditure Panel Survey (MEPS) datasets to quantify the increased likelihood of hospitalization for US users of opioids, concurrent opioid and benzodiazepine use (commonly called "double-threat"), and opioid, benzodiazepine, and muscle relaxant use ("triple threat") compared to a reference group of nonusers of these agents in the United States.[12]

Methods

The 2013 and 2014 MEPS-Panel 18 longitudinal dataset and affiliated Prescribed Medicines Files were used for this retrospective analysis.[13] The MEPS database was designed and validated to produce a national reflection of family and individual health services usage for people living in the United States.[14] The MEPS Household Component files are data from a sample of families and individuals in selected communities across the United States, drawn from a nationally representative subsample of households that participated in the National Health Interview Survey from the prior year.[15] The cohort surveyed in MEPS has been weighted to be reflective of the actual US population in the years 2013 and 2014. The finalized analysis dataset was used to quantify the relationship between opioid, benzodiazepine, muscle relaxant, double-threat, and triple-threat usage and odds of hospitalization in people living in the United States.

Longitudinal Analysis of Benzodiazepine, Opioids, and Muscle Relaxant Usage

The prescribed medicines in MEPS were combined with the longitudinal MEPS-Panel 18 by linking study subject numbers. Medications that were not designated as muscle relaxants, benzodiazepines, and opioids were removed from the medication list for this study. All prescriptions of the same medications prescribed per patient within a specified round were summed to provide total day supply per round by dividing total dose quantity per round by defined daily dose for each study medication.[16]

Prevalence Estimation of "Double-Threat" and "Triple-Threat"

Using the finalized analysis set, concurrent use of muscle relaxants, benzodiazepines, and/or opioids were categorized as either "double-threat" and/or "triple-threat." Concurrent use of opioids and benzodiazepines was defined as "double-threat" and the concurrent use of opioids, benzodiazepines, and muscle relaxants as "triple threat."

Association of Medication Exposures With Hospitalizations

Separate analyses were performed to measure the association via odds ratio (OR) between exposures of opioids, benzodiazepines, muscle relaxants, double-threat, and triple-threat using a reference group of nonusers of these medications with the outcome of hospitalization. To evaluate the relationship within the same year of exposure and outcome, we completed an analysis of 2013 exposure and 2013 outcome and performed a separate analysis of 2014 exposure and 2014 outcome. Finally, to examine the relationship of prior year exposure of the study medications to hospitalization in the succeeding year, the association was measured of 2013 medication exposure with hospitalization in 2014.

Statistical Analysis Plan

Logistic regression applying the subject-level MEPS survey weights was performed to measure association via ORs of medication exposures with the outcome of all-cause hospitalization. Study subjects were categorized into exposure groups as nonusers (nonuse of opioids, benzodiazepines, or muscle relaxants), opioid users, benzodiazepine users, muscle relaxant users, double-threat users, and triple-threat users. For purposes of regression analysis estimation function, all exposure groups were mutually exclusive. Analyses were conducted using RStudio® 1.1.5 (Boston, MA) with α level $= 0.05$ for all comparisons.

Results

Prevalence Analysis

A total of 16 715 individuals were survey-weighted to represent the US population of 321 million in 2013. Of the 16 715 individuals, 9857 were between 18 and 64 years of age representing a population of approximately 196 million or 61.4% of the total population. Of the 321 million represented, 2.28 million (0.7%) individuals had missing age values. Opioids, benzodiazepines, and muscle relaxants were prescribed in 11.9% (38.4 million lives), 4.2% (13.5 million),

and 3.4% (10.9 million), respectively, of the individuals in 2013 and 12.2% (39.3 million), 4.6% (14.8 million), and 3.6% (11.6 million), respectively, in 2014. In 2013, 1.6% of the population were on double-threat and 0.53% of the population were on triple threat. In 2014, 1.9% of the population are on double-threat and population on triple threat remained at 0.53%.

Of the 9961 medication records in the study sample, 62.3% were opioids, 21.9% were benzodiazepines, and 15.8% were muscle relaxants. A total of 49 (0.5%) medication records were omitted due to missing medication quantity. Average days' supply per patient in 2013 for opioids was 18.9 days and in 2014 was 19.22 days. The average days' supply per patient was 39.9 days in 2013 and 41.7 days in 2014 for benzodiazepines. Muscle relaxants' average days' supply in 2013 was 27.8 days and in 2014 was 31.8 days.

Comparing 2013 to 2014, the prevalence of double-threat patients rose from 5.13 million lives (1.59%) to 6.21 million lives (1.93%), while the prevalence of triple-threat users remained unchanged at 1.71 million lives (0.53%).

2013 Analysis

Patients on any of the study medications, double-threat, and triple-threat were at increased probability of same year hospitalization in 2013 compared to individuals not using these medications with triple-threat users at highest likelihood of same year hospitalization. Opioid users had an OR of 5.63 (95% confidence interval [CI]: 5.62-5.64). Benzodiazepine users had an OR of 3.67 (95% CI: 3.66-3.68). Muscle relaxant users had an OR of 2.42 (95% CI: 2.41-2.43). Double-threat users had an OR of 5.71 (95% CI: 5.69-5.72). Triple-threat users had an OR of 8.52 (95% CI: 8.50-8.55; Table 1).

2014 Analysis

Similar to 2013 findings, patients on any of the study medications, double-threat, and triple-threat were at increased probability of same year hospitalization in 2014 compared to individuals not using these medications. Opioid users had an OR of 6.72 (95% CI: 6.71-6.73). Benzodiazepine users had an OR of 3.43 (95% CI: 3.42-3.44). Muscle relaxant users had an OR of 1.11 (95% CI: 1.10-1.11). Double-threat users had an OR of 11.47 (95% CI: 11.44-11.49). Triple-threat users had an OR of 5.06 (95% CI: 5.04-5.08; Table 1).

2013 to 2014 Longitudinal Analysis

Patients exposed to the high-risk study medications in 2013 were at elevated likelihood in the following year compared to those not on any of these medications. Opioid users had an OR of 2.32 (95% CI: 2.32-2.32). Benzodiazepine users had an OR of 3.11 (95% CI: 3.10-3.12). Muscle relaxant users had an OR of 2.37 (95% CI: 2.36-2.38). Double-threat users had an OR of 5.59 (95% CI: 5.57-5.60). Triple-threat users had an OR of 4.61 (95% CI: 4.59-4.63; Table 1).

Discussion

For the endpoint of hospitalization, this is the first comprehensive outcomes study of the additive probability for patients with combined use of opioids, benzodiazepines, and muscle relaxants using a US-representative, validated, longitudinal database from HHS. While a limited number of published studies have investigated the pharmacodynamics salient to the additive toxicity of combined use of opioids, benzodiazepines, and/or muscle relaxants, no health services utilization studies have been completed.[17,18] Exposure to the multiple potentially inappropriate medications increased hospitalization probability for patients. In 2013 and 2014, patients on triple-threat had a minimum fourfold increased odds of hospitalization compared to nonusers.

A limited set of prior studies have evaluated the additive risks of prescribing benzodiazepine to patients on opioids. The addition of concurrent muscle relaxant usage has not been assessed to our knowledge for hospitalization endpoints in a US national database. With growth in the number of prescriptions for benzodiazepines by 67% from 1996 to 2013, the likelihood of concurrent use of opioids and benzodiazepines medications has also increased.[17,19] Over the last decade, deaths involving opioid overdose have more than doubled leading to 28 647 deaths in 2014 alone.[20] This number increased to more than 42 000 deaths in 2016.[21] Escalating concurrent use of opioids, benzodiazepines, and muscle relaxants portends growing risk of death due to additive CNS and respiratory depression. To control combined CNS depressant use, the FDA has issued a boxed warning for combined benzodiazepine and opioid use.[22] Both the Centers for Medicare and Medicaid Services (CMS) and the CDC have initiated monitoring programs to detect and prevent avoidable concurrent use of multiple CNS depressant medications.[23,24]

Several state-wide protocols and regulations have been established to reduce the inappropriate use of these medications. The State of California has established a mandatory prescription drug monitoring program (PDMP) to track patients' dispensed controlled substances. The California PDMP referred to as "The Controlled Substance Utilization Review and Evaluation System" (CURES) documents patients' dispensed controlled substances in the prior years to provide clinicians a resource to monitor medication dispensing for possible risks. As implementation of this system, CURES has been bolstered for integration in pharmacies both inpatient and outpatient. Although CURES functions as a record of the patterns of patients' prescribed medications, this PDMP does not immediately alert the provider nor the pharmacy of any concurrent use of these high-risk medications.[25-26] Thus, medication reconciliation to address double threat and triple threat remains constrained to the prescribers' awareness and discretion.

Table 1. Matrix of Odds Ratios for Hospital Discharge (HD) by Exposure, Comparator, and Year.

			Exposure group					
Overall patient			No medication	Muscle relaxant	Benzodiazepine	Opioid	Double threat	Triple threat
Control Group	No medication	2013 exposure w/ 2013 HD visit ≥1		2.42 (2.41-2.43)	3.67 (3.66-3.68)	5.63 (5.62-5.64)	5.71 (5.69-5.72)	8.52 (8.50-8.55)
		2014 exposure w/ 2014 HD visit ≥1		1.11 (1.10-1.11)	3.43 (3.42-3.44)	6.72 (6.71-6.73)	11.47 (11.44-11.49)	5.06 (5.04-5.08)
		2013 exposure w/ 2014 HD visit ≥1		2.37 (2.36-2.38)	3.11 (3.10-3.12)	2.32 (2.32-2.32)	5.59 (5.57-5.60)	4.61 (4.59-4.63)
	Muscle relaxant	2013 exposure w/ 2013 HD visit ≥1			1.52 (1.51-1.52)	2.33 (2.32-2.33)	2.36 (2.35-2.37)	3.52 (3.51-3.54)
		2014 exposure w/ 2014 HD visit ≥1			3.10 (3.08-3.12)	6.07 (6.04-6.10)	10.36 (10.30-10.41)	4.57 (4.54-4.60)
		2013 exposure w/ 2014 HD visit ≥1			1.31 (1.31-1.32)	0.98 (0.98-0.98)	2.36 (2.35-2.37)	1.95 (1.94-1.96)
	Benzodiazepine	2013 exposure w/ 2013 HD visit ≥1				1.53 (1.53-1.54)	1.55 (1.55-1.56)	2.32 (2.31-2.33)
		2014 exposure w/ 2014 HD visit ≥1				1.96 (1.95-1.96)	3.34 (3.33-3.35)	1.48 (1.47-1.48)
		2013 exposure w/ 2014 HD visit ≥1				0.75 (0.74-0.75)	1.80 (1.79-1.80)	1.48 (1.48-1.49)
	Opioids	2013 exposure w/ 2013 HD visit ≥1					1.01 (1.01-1.02)	1.51 (1.51-1.52)
		2014 exposure w/ 2014 HD visit ≥1					2.42 (2.40-2.42)	0.75 (0.75-0.76)
		2013 exposure w/ 2014 HD visit ≥1					2.41 (2.40-2.42)	1.99 (1.98-2.00)
	Double threat	2013 exposure w/ 2013 HD visit ≥1						1.50 (1.49-1.50)
		2014 exposure w/ 2014 HD visit ≥1						0.44 (0.44-0.44)
		2013 exposure w/ 2014 HD visit ≥1						0.83 (0.82-0.83)
	Triple threat	2013 exposure w/ 2013 HD visit ≥1						
		2014 exposure w/ 2014 HD visit ≥1						
		2013 exposure w/ 2014 HD visit ≥1						

Other states have developed approaches to minimize opioid- and benzodiazepine-associated risks such as alternate monitoring systems and/or educating practitioners.[27-29] Multiple managed health care organizations have implemented medical electronic alerts as surveillance strategies to improve medication safety.[30,31] Other investigators have suggested that extending default monitoring to the Medicare population would greatly aid in detection to facilitate individualized care to prevent double threat and triple threat. Finalization of new CMS policies to prevent opioid overuse is expected in 2019.[23] Expansion of surveillance efforts from the state to national level may also harmonize state-wide health care systems and decrease gaps in care coordination.

Review and identification of existing medications should be undertaken prior to the initiation of a new opioid, benzodiazepine, or muscle relaxant for any patient. This may involve usage of a PDMP or review of available administrative claims data to detect potentially offending medications. Within the electronic medical record, an automated alter would inform the prescriber or their care team of the synergistic risk of adding the agent to the current regimen. For patients, based on the evidence, that are deemed necessary for prescribing of a double-threat or triple-threat regimen, the care plan *a priori* should feature an automatic monthly follow-up to ensure successful management of measurable symptom outcomes and gradual dose reduction or de-prescribing if possible. Confirmation of patient understanding via pharmacist consultation of treatment goals, potential risks, adverse events, including availability of opioid overdose reversal agents, must also be built in to the default treatment path. Shared decision making for the medication action plan and overall care plan will help empower the patient to state their own treatment goals for these medications and embolden honest dialogue about benefits and potential risks.

Additional efforts are warranted to ensure that usage of opioids, benzodiazepines, and muscle relaxants and any concurrent use is clinically necessary. Gradual dose reduction and de-prescribing protocols have been converted to quality indicators by organizations such as the Pharmacy Quality Alliance that are being used by CMS in the Medicare Patient Safety Reports and in the Medicaid Adult Core Set that began in 2018. Specifically, CMS has begun to report the percentage of patients 18 years and above with concurrent use of prescription opioids and benzodiazepines for 30 or more cumulative days.[32]

Limitations

This is a survey-based analysis and thus potentially subject to reporter error. However, MEPS is a validated database sponsored by the Agency for Health care and Quality of HHS and is routinely applied for national estimation by researchers and the federal government for clinical and policy-level decision making. The analysis endpoint was hospitalization attributable to any cause as the MEPS database does not specify the source offending agent. Hence, the association outcome was all-cause hospitalization. *A priori*, the study aim was to delineate the increased likelihood of any hospitalization for those consuming concomitant high-risk medications.

Conclusions

Patients on triple-threat and double-threat experienced a greater likelihood of hospitalization compared to non-users. The addition of muscle relaxant to double-threat users increased hospitalization probability compared to those on double threat. Amplified national efforts in medication surveillance and data-driven prescribing and follow-up monitoring for concurrent opioid, benzodiazepine, and muscle relaxant use are needed to reduce this public health threat.

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