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Title: Impact of benzodiazepines and polysubstance status on repeat non-fatal drug overdoses

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Abstract

Research has shown that benzodiazepines and mental health disorders can increase the likelihood of repeat overdose, but researcher have not explored this association in Tennessee (TN). We examined benzodiazepines, polysubstance overdose status with/without benzodiazepines, and mental health comorbidities with repeat overdose using statewide data in TN. This study analyzed TN hospital discharge data on nonfatal overdoses for patients ages 18–64 from 2012 to 2016 for 21,066 patients with an initial inpatient visit and 36,244 patients with an initial outpatient visit. The study assessed each patient at one year after initial overdose to determine likelihood of repeat overdose. We used a Cox proportional hazards model to compute hazard ratios (HRs) and 95% confidence intervals (CIs) to determine the factors associated with repeat nonfatal overdose. Repeat overdose rates, by one year after index overdose, were 12.9% of the sample for inpatients and 13.9% of the sample for outpatients. The visit factors (overdose characteristics and comorbidities determined from the initial visit) that the study found to be independently associated with repeat overdoses among inpatients were polysubstance status (HR: 0.88, 95% CI 0.78–0.99), benzodiazepine/polysubstance interaction (HR: 1.29, 95% CI 1.02–1.64), and presence of any mental health disorder (HR: 1.28, 95% CI: 1.18–1.39). For outpatients, the benzodiazepine/polysubstance interaction (HR: 1.21, 95% CI 1.01–1.44) was significant without adjusting for demographic factors. We found evidence that benzodiazepine/polysubstance status and mental health disorders were associated with repeat overdose for inpatients, and that benzodiazepine/polysubstance status was associated with repeat overdose for outpatients. Findings support the need to include polysubstance status and mental health in overdose prevention efforts.

Keywords: Overdose; Polysubstance; Benzodiazepines; Nonfatal; Mental health; Comorbidity

Abbreviations

CDC: Centers for Disease Control and Prevention

CIs: Confidence Intervals

DEA: Drug Enforcement Administration

ICD: International Classification of Diseases

HCUP: Healthcare Cost and Utilization Project

HDDS: Hospital Discharge Data System

HRs: Hazard Ratios

TDH: Tennessee Department of Health

1. Introduction

Tennessee (TN) is one of the many states currently facing an opioid crisis and rising drug overdose rates. The state's all drug overdose death rate continues to increase, from 17.0 per 100,000 residents in 2012 to 26.6 per 100,000 residents in 2017 (Tennessee Department of Health, 2018b, 2019), Nonfatal overdose rates in TN have also been increasing for outpatient visits, which are mainly emergency department visits. In 2012, the age-adjusted all drug overdose outpatient visit rate was 210.4 visits per 100,000 residents, increasing to 246.3 per 100,000 in 2017 (Tennessee Department of Health, 2018b, 2019). Polysubstance overdose death rates in the state have been increasing at a quicker pace than non-polysubstance overdose deaths (Golladay, Donner, & Nechuta, 2020), with 66.5% of all overdose deaths and 79% of opioid overdose deaths in 2017 involving more than one drug (Tennessee Department of Health, 2019). While studies have described factors associated with fatal and nonfatal overdoses in the state (Golladay et al., 2020; Krishnaswami, Mukhopadhyay, McPheeters, & Nechuta, 2020; Tennessee Department of Health, 2019), research has not explored factors leading to repeat overdose, and the role of polysubstance use in repeat overdose.

Repeat overdoses are associated with substantial morbidity and increased risk of death (Darke et al., 2014; Zibbell, Howard, Duhart, Ferrell, & Karon, 2019). The national estimated burden of opioid overdoses and dependence in 2013 was $78.5 billion, with 25% of the cost falling on the public through health care, treatment, and criminal justice costs (Florence, Zhou, Luo, & Xu, 2016). Through identification of patients at risk of repeat overdose and targeted care, substantial patient morbidity and cost burden to the state could be potentially mitigated. Previous literature on factors associated with repeat drug overdoses has largely focused on opioid use; however, benzodiazepine use has been found to increase the risk of repeat overdose, especially in combination with opioids, potentially due to the respiratory depressive effect caused by combined use (Jann, Kennedy, & Lopez, 2014; Jones & McAninch, 2015; Olfson, Wall, Wang, Crystal, & Blanco, 2018). Further, as benzodiazepines are often prescribed for muscle spasms associated with chronic pain, the risk of overdose is known to be greater among patients with chronic pain (Drug Enforcement Administration, 2017; Sun et al., 2017). Benzodiazepines are also prescribed for mental health conditions such as anxiety and insomnia (Drug Enforcement Administration, 2017), which may partly explain the increased likelihood of repeat overdose among patients with psychiatric disorders (Brady, Giglio, Keyes, DiMaggio, & Li, 2017; Olfson et al., 2018).

To address the limited data on risk factors for repeat overdose that go beyond opioid use, we

conducted the first study in TN to understand the effects of a prior polysubstance overdose, benzodiazepine involvement, and mental health disorder status on risk of repeat overdoses. We hypothesized that the presence of benzodiazepines and a polysubstance initial overdose increases the risk of repeat nonfatal overdose within one year of index overdose independent of demographic variables and mental health status, for both inpatient and outpatient hospital visits. Previous studies have included only subsets of patients (Medicare, Medicaid, or veterans) as opposed to all at-risk adult patients, have only considered opioid overdoses and not all drug overdose types, and have not considered polysubstance overdoses beyond the opioids and benzodiazepines combination (Jann et al., 2014; Jones & McAninch, 2015; Olfson et al., 2018; Park, Saitz, Ganoczy, Ilgen, & Bohnert, 2015; Sun et al., 2017).

2. Materials and methods

2.1. Data source and sample

The study extracted the sample from the TN 2012–2017 Hospital Discharge Data System (HDDS) to conduct a retrospective longitudinal cohort study. The study evaluated patients who had a drug overdose between 2012 and 2016 at one year (365 days) after index overdose to assess repeat events. A flow chart describing sample derivation is shown in Figure 1. The HDDS is based on mandatory submissions from all hospitals licensed by the Tennessee Department of Health (TDH), which includes information about each hospital discharge. The data are submitted according to the UB-04 format established by the National Uniform Billing Committee. Available patient characteristics included race, gender, payer type, and age. Identifiers for matching multiple discharge records to the same patient (as applicable) included patient's name, date of birth, and address. HDDS billing records include up to 18 diagnosis codes and up to three external cause of injury (ECI) codes. (Tennessee Department of Health, 2018a) The study time period included International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes. Prior to October 2015, the study used ICD-9-CM codes, and after this date the study used ICD-10-CM codes. The study used ICD codes to identify the initial population of all-drug overdoses, as well as subsequent overdoses and comorbidities using validated codes (see Tables 1 and 2), described in detail here. We obtained TDH IRB approval for this analysis.

[Insert Figure 1 here]

Patients excluded from the analysis were non-TN residents and patients who died during the visit or subsequent overdoses. The study excluded any discharges from federal, rehabilitation, or psychiatric

hospitals due to incomplete data.

A total of 128,613 overdose discharges of TN residents from nonfederal acute care hospitals from 2012 to 2017 were available for analysis. There were 74,173 discharges from patients between 18 and 64 years of age at first overdose visit between 2012 and 2016 (hereafter, first overdose visit is referred to as "first visit"). This study included a total of 57,310 patients with first overdose visit in this analysis, comprising 21,066 inpatients (36.8%) and 36,244 outpatients (63.2%).

2.2. Variables

2.2.1. Outcome variables

Patients with multiple events were those who had more than one visit during the year following the first overdose event for any type of overdose, regardless of drug class. The study identified duplicates using SAS Dataflux Data Management Studio (SAS Institute, 2016) using clean and standardized name and date of birth fields (e.g., removed spaces, symbols, and inaccurate text), and validated with social security number or a geocoded address (addresses were geocoded in ArcGIS, version 10.6) (ESRI, 2018). Details of data linkage methodology have been reported previously (Nechuta, Mukhopadhyay, Krishnaswami, Golladay, & McPheeters, 2019). Briefly, the study gave each patient a cluster identification number from this process. The study used this identification number to sort visits by patient and by discharge date, with the earliest discharge date during the study period defining the first visit.

The study separated patients for analysis by their visit type at first visit in the study period, as previous research has suggested outpatient treatment increases likelihood of repeat overdose (Olfson et al., 2018). Repeat overdoses could be either visit type among the study population. The study defined visit type by the hospital discharge system, in which inpatient visits are hospitalizations lasting longer than 24 hours, while outpatient visits are less than 24 hours. Outpatient visits are typically emergency department visits but can include any observation period 23 hours or less, ambulatory surgeries, or diagnostic services such as CT scans or MRIs. If a patient presents to an outpatient setting but is then admitted, the visit is counted as an inpatient hospitalization. Approximately 98% of outpatient visits are emergency department visits (Tennessee Department of Health, 2018a).

2.2.2. Health-related independent variables

To identify overdose-related variables, the study used established ICD codes (Appendix Table A1). Study staff checked all 21 fields (both the 18 diagnostic codes and 3 ECI codes) for benzodiazepine involvement and polysubstance overdose status. The study defined a polysubstance overdose as having

more than one of the following categorizations of overdose: nonheroin opioid, heroin, benzodiazepine, stimulant, other drug, and alcohol poisoning. The study defined "other drug" overdoses as an overdose code that was included in the "all drug" overdose codes but was not included in the nonheroin opioid, heroin, benzodiazepine, stimulant, or alcohol poisoning categories. The study only captured alcohol poisoning as co-occurring with all drug nonfatal overdoses. For ICD-10 years, the study included only intent codes 1–4 (accidental, intentional, assault, and undetermined) and initial or missing/unspecified overdose encounters (Centers for Disease Control and Prevention, 2018). The study coded all overdose-related factors as a binary variable (present/absent).

The study used valid ICD diagnosis codes to classify patients as having one or more mental health comorbidities (Appendix Table A2). The study used codes provided by Quan et al. (Quan et al., 2005) as a starting point, with additional codes added based on clinical classifications from the Healthcare Cost and Utilization Project (Elixhauser, Steiner, & Palmer, 2015; Healthcare Cost and Utilization Project, 2017). The study defined comorbid conditions as those present at or identified while receiving treatment for the first overdose visit. The study defined psychiatric disorders separately for descriptive purposes as "depression", "anxiety", "post-traumatic stress disorder", "schizophrenia", and "other mood disorders". For the analysis, we combined the presence of any of these disorders to create an "any mental health" variable. The study excluded other psychiatric disorders from analysis due to small frequency in sample.

2.2.3. Demographic independent variables

The study used demographic variables that were part of the hospital record, defined based on the patient's first visit during the study period, as predictors of repeat overdose, including gender (male/female), age in years (categorized as 18–24, 25–44, and 45–64), race (White/Caucasian, Black/African American, Native American/Alaskan Native, Asian/Pacific Islander, other race, and unknown), and year of initial overdose (2012–2016). We considered only patients between the ages of 18 and 64 (at first visit) for analysis, as national trends of low overdose rates below age 15 and over age 64 merits an exclusion criterion to reduce underpowered statistical analyses due to small sample size (Centers for Disease Control and Prevention, 2019). Due to small cell sizes in certain categories, the study recoded race to White/Caucasian and non-White. Although previous research has suggested that more overdoses occur around metropolitan areas as opposed to rural areas (Boscarino et al., 2016), drug overdose death rates are rapidly increasing in rural areas (Mack, Jones, & Ballesteros, 2017; Paulozzi et al., 2012). To assess the effect of urbanization on TN's overdose rates, the study categorized

patient's county of residence by size of metropolitan area using the National Center for Health Statistics 2013 urban-rural classification scheme to create region of residence (Ingram & Franco, 2014). The study classified ethnicity status as Hispanic or non-Hispanic and classified as Medicare, Medicaid, Commercial, Other Government (not Medicare/Medicaid), cash/self-pay, medically indigent/free, and other/unknown. Variables used for descriptive purposes only were year of initial overdose, ethnicity, and payer. The breakdown of demographic variables and visit factors by first visit type are described in Table 1, with any missing values excluded.

2.3. Statistical analysis

The study calculated descriptive statistics (frequency and proportions) for the basic demographic, clinical, and outcome characteristics for the whole sample. Study staff conducted chi-square tests on all model variables to determine significant differences between single and multiple event patients, for both initial outpatient and initial inpatient visits. We used cell chi-square values to determine directionality. To identify factors associated with multiple overdose events versus a single event, we generated a Cox proportional hazards model to estimate hazard ratios (HRs) and 95% confidence intervals (CI). The study censored subjects if they did not have a subsequent overdose event within one year of their index overdose. The study tested the proportional hazards assumption for all independent variables by examining interaction terms for each covariate and survival time. We added any significant interactions to the final model (Allison, 2010). The study used Kaplan-Meier product-limit estimates to generate cumulative incidence curves. Study staff conducted a log-rank test to assess differences in event occurrence across levels of the interaction. The analysis included models with only the visit factors, and then models adjusting for demographic characteristics. The study excluded patients with missing values for the model factors in the modeling process.

All analysis took place at the patient level. The study conducted modeling and coding for factors in SAS v9.4 (SAS Institute, 2012). All HRs presented are adjusted for variables listed in the tables. The study considered P-values < 0.05 statistically significant.

3. Results

3.1. Sample description

Data were available for analysis from 21,066 initial inpatient and 36,244 initial outpatient overdose visits. There were three inpatients and six outpatients missing values for race and region of residence. Among patients with a polysubstance overdose, benzodiazepine involvement was significantly higher for patients with multiple events (inpatients: $p < .001$, outpatients: $p < .05$). The study

saw this increase in both the inpatient setting (multiple: 66.7%, single: 59.6%) and outpatient setting (multiple: 61.6%, single: 58.3%). There was no significant difference in benzodiazepine involvement across event types for non-polysubstance overdoses. (Figure 2).

[Fig. 1: Benzodiazepine involvement by polysubstance status.]

3.1.1. Inpatients

The majority of the inpatient sample was White, non-Hispanic, between ages 45 and 64, and from a large metropolitan area. The study found significant differences between event types for race, age, and year of initial overdose. Multiple visit patients had significantly higher than expected values for White race ($p < .0001$), the 45–64 year age group ($p < .01$), and the 2012 year of initial overdose ($p < .0001$). Sex and region type did not differ across event type, and the study did not test ethnicity due to small cell values. The most common payer for single visit patients was cash/self-pay at 26.2%, while the most common payer for multiple visit patients was Medicare at 33.9%. Multiple visit patients tended to use Medicare and Medicaid, while single visit patients showed higher percentages of cash/self-pay and commercial insurance. Multiple event patients had significantly higher than expected values for presence of benzodiazepines ($p < .001$), presence of any mental health disorder ($p < .001$), and absence of alcohol poisoning ($p < .05$). Polysubstance status did not show significant differences across event type. The most common mental health disorder across settings was depression. Patients were similar across the categories of mental health disorders, with the exception of mood disorders and anxiety/post-traumatic stress disorders, where multiple visit patients had much higher percentages than single visit patients. (Table 1)

[Table 1. TN HDDS (2012_2016): Factors by event type (single vs. multiple nonfatal overdose[s]) for all drug overdoses – inpatient and outpatient.]

3.1.2. Outpatients

The majority of the outpatient sample was White, non-Hispanic, between ages 25 and 44, and from a large metropolitan area. The study found significant differences between event types for race, age, sex, region type, and year of initial overdose. Multiple visit patients had higher than expected values for White race ($p < .0001$), the 45–64 year age group ($p < .001$), male sex ($p < .05$), nonmetropolitan area residents ($p < .0001$), and the 2012 year of initial overdose ($p < .01$). The study did not test ethnicity was due to small cell values. The most common payer for single visit patients was cash/self-pay at 28.1%, while the most common payer for multiple visit patients was Medicaid at 28.7%. Percentages were similar across settings, although single visit patients had higher instances of

commercial insurance and multiple visit patients had more usage of Medicare. Multiple event patients had significantly higher than expected values for presence of benzodiazepines, and polysubstance overdose status. The most common mental health disorder for both settings was depression. Patients were similar across all categories of mental health disorders (Table 1).

3.2. Visit factors only model by visit type

As shown in Table 2, patients with a polysubstance index overdose in an inpatient setting were slightly less likely when compared to patients without polysubstance index overdose to have a repeat overdose within one year (HR: 0.88, 95% CI: 0.78–0.99). Patients with a polysubstance overdose that involved benzodiazepines were more likely to have a repeat overdose than patients without benzodiazepine involvement and a polysubstance overdose (HR: 1.29, 95% CI: 1.01–1.63). Inpatients with the presence of any of the study mental health disorders (depression, anxiety/post-traumatic stress, schizophrenia, mood disorders) at first visit were 1.3 times more likely than patients without mental health disorders to have another overdose (HR: 1.31, 95% CI: 1.21–1.42). Patients with a polysubstance index overdose in an outpatient setting that involved a benzodiazepine were approximately 1.2 times more likely to have a repeat overdose than patients with a non-polysubstance index overdose within one year of the index overdose (HR: 1.21, 95% CI: 1.01–1.44). Outpatients with the presence of any of the study mental health disorders (depression, anxiety/post-traumatic stress, schizophrenia, mood disorders) at first visit were less likely to have a repeat overdose within one year (HR: 0.86, 95% CI: 0.80–0.93).

[Table 2. Adjusted hazard ratios (HRs) for repeat nonfatal overdose within first year following nonfatal overdose, HDDS 2012–2016]

3.3. Full model by visit type

Table 2 shows the factors associated with repeat overdose within one year after the index overdose. Inpatients with a polysubstance overdose were slightly less likely to have a repeat overdose within one year than patients with a non-polysubstance overdose (HR: 0.88, 95% CI 0.78–0.99). Patients with a polysubstance overdose that involved a benzodiazepine were more likely to have a repeat overdose within one year than patients without benzodiazepine involvement and polysubstance overdose (HR: 1.29, 95% CI 1.02–1.64). Inpatients with any comorbid mental health disorder at index overdose were approximately 1.3 times more likely to have another overdose event within one year than patients without a comorbid mental health disorder (HR: 1.28, 95% CI: 1.18–1.39). Male inpatients

were slightly more likely than female inpatients to have a repeat overdose (HR: 1.15, 95% CI: 1.03, 1.30). Inpatients between the ages of 18 and 24 were less likely than older adults (ages 45–64) to have a repeat overdose (HR: 0.82, 95% CI 0.72–0.94). Non-White inpatients were less likely to have a repeat overdose than White inpatients (HR: 0.70, 95% CI: 0.62-0.79). Sex and region of residence were not significantly associated with repeat nonfatal overdose.

Outpatients with any comorbid mental health disorder at index overdose were less likely to have another overdose event within one year than patients without a comorbid mental health disorder (HR: 0.83, 95% CI: 0.77–0.90). Non-White outpatients were less likely to have a repeat overdose than White outpatients (HR: 0.57, 95% CI: 0.52–0.63). When compared to patients from a rural area, all sizes of metropolitan areas were less likely to have a repeat overdose [small metropolitan area (HR: 0.56, 95% CI: 0.50–0.63), medium metropolitan area (HR: 0.53, 95% CI: 0.49–0.57), large metropolitan area (HR: 0.51, 95% CI: 0.46–0.55)].

The incidence rate of repeat overdose over time for inpatients is shown in Figure 3. For inpatients, the overall log-rank test was significant ($\chi^2 = 18.22$, $p < .001$), showing differences across strata without adjusting for demographic factors. Patients with benzodiazepines alone and patients with a polysubstance overdose without benzodiazepine involvement both showed a significantly lower incidence rate than patients with a polysubstance overdose with benzodiazepine involvement [benzodiazepines alone ($\chi^2 = 8.98$, $p < .01$), polysubstance overdose ($\chi^2 = 18.20$, $p < .0001$)]. The incidence rates for patients were: 13.5% for a non-polysubstance overdose without benzodiazepine involvement, 13.0% for benzodiazepine involvement alone, 11.1% for a polysubstance overdose without benzodiazepine involvement, and 14.5% for patients with a polysubstance overdose and benzodiazepine involvement.

The incidence rate of repeat overdose over time for outpatients is shown in Figure 4. For outpatients, the overall log-rank test was significant ($\chi^2 = 36.04$, $p < .0001$), showing differences across strata without adjusting for demographic factors. All levels showed significantly lower incidence rates than patients with the presence of benzodiazepines and polysubstance status. The incidence rates for patients were: 13.4% for a non-polysubstance overdose without benzodiazepine involvement, 13.0% for benzodiazepine involvement alone, 14.6% for a polysubstance overdose without benzodiazepine involvement, and 16.4% for patients with a polysubstance overdose and benzodiazepine involvement.

[Fig. 3: TN HDDS (2012–2016): Cumulative incidence rate of repeat overdose over time – inpatients.]

[Fig. 4: TN HDDS (2012–2016): Cumulative incidence rate of repeat overdose over time – outpatients.]

4. Discussion

In this large statewide study utilizing hospital billing data, we found that the combination of a benzodiazepine with other drugs was associated with increased likelihood of overdose for inpatients and outpatients, without adjusting for demographic factors. This is consistent with the known respiratory depressive effect of benzodiazepines in combination with opioids (Jann et al., 2014). Our findings are also consistent with previous studies that have shown past year benzodiazepine use to significantly increases the risk of nonfatal overdose (Thylstrup, Seid, Tjagvad, & Hesse, 2020). When adjusting for demographic factors, the interaction remained significant only for inpatients. This may be due to the variation in visits among outpatients, as well as the limited time period for assessment. Overall, patients with an increased likelihood of repeat overdose tended to be White and older in age. Inpatients with increased likelihood of repeat overdose tended to be males. Outpatients with increased likelihood of repeat overdose tended to be from rural areas. The age, race, and the sex associations for inpatients correspond with prior overdose research in TN and nationally (Brady et al., 2017; Tennessee Department of Health, 2019). The association of repeat overdose with rural areas for outpatients is consistent with the rising overdose rates in rural areas (Mack et al., 2017), despite higher rates of overdose around metropolitan areas (Boscarino et al., 2016).

Mental health disorders significantly increased the likelihood of repeat overdose for inpatients, but significantly decreased the likelihood of repeat overdose for outpatients. The inverse association with outpatients may be due to the variation in reason for visits, or less completed record collection for mental health conditions in an ER setting. Inpatients also typically represent more serious cases, which may have contributed to the different findings. The likelihood of repeat overdose for patients with mental health disorders may have been underestimated due to lack of information, as mental health disorders are more common among substance use patients (Substance Abuse and Mental Health Services Administration, 2018). A retrospective cohort of patients aged 19–64 in Japan found that as dosage of benzodiazepine prescriptions increased, risk of subsequent nonfatal overdose increased (Okumura & Nishi, 2017). Specifically, patients with recent prescriptions for high levels of benzodiazepines are 1.4 times more likely to have a subsequent overdose; when patients do not have recent psychiatric treatment, they are 1.6 times more likely to have a repeat overdose (Okumura &

Nishi, 2017). Additionally, our definition of any mental illness as including depression, anxiety/post-traumatic stress, schizophrenia, and mood disorders may have been too broad.

Both inpatients and outpatients showed nonproportional hazard rates. This was the result of sex being time-dependent for inpatients, and any mental health disorder and region being time-dependent for outpatients. Prior to adjusting for the nonproportional effects of sex for inpatients and mental health disorders for outpatients, these effects were not significant. After adjusting for nonproportionality, the coefficients for region of residence and mental health decreased, while the coefficient for sex increased. However, other coefficients showed little to no change.

This is the first study in TN to identify factors associated with nonfatal repeat overdose events. Study strengths include the large sample representing five years of data, assessing all patients within one year after initial overdose, and inclusion of all payer types. The focus on polysubstance overdose status as opposed to assigning a primary drug type to each overdose or investigating one type of overdose allows more targeted data to identify at risk patients, in particular due to the increasing concern of polysubstance use in the U.S. Information about the role of benzodiazepines and polysubstance overdose status in repeat overdose cases could better identify candidates for referral to treatment and increase the quality of provider education. Additionally, the separation of inpatients and outpatients helps to provide data to establish specific protocols for patients in each setting, as inpatients and outpatients showed differing patterns of association. These different associations can help providers and health department officials to further understand repeat overdose patterns and how to intervene, which can be disseminated via trainings and informational documents. Although nonfatal benzodiazepine overdose rates are declining, benzodiazepines were involved in 12.2% of nonfatal overdoses in 2017 (Vivolo-Kantor et al., 2020). Further, while opioid prescription rates have significantly declined over time due to new state policies such as the 2012 Prescription Safety Act and the 2016 Prescription Safety Act, benzodiazepine prescription rates have not shown a drastic decrease (Tennessee Department of Health, 2019). Therefore, patients with benzodiazepine prescriptions may need to be monitored more closely. If these efforts to more closely monitor are successful, the costs to federal and state programs could be reduced, as more than 40% of study patients across settings utilize a government-funded payer (Medicare, Medicaid, other government). Previous work in the state has shown that prescriptions for controlled substances decrease after any drug overdose type; additionally, inpatients used benzodiazepine prescriptions at higher rates after drug overdose (Krishnaswami et al., 2020). Future research could link the discharge information and multiple event status to the prescription

drug database, death records, and electronic health records to provide further knowledge that could guide policy.

4.1. Limitations

Results are limited to discharges from TN acute care hospitals for the first nonfatal drug overdose during the study period, and may not be generalizable to populations that have repeat overdoses or other states with different demographic profiles. Since this is a population-based study with a one-year follow-up period, we may not have captured a patient's true first overdose or any subsequent overdoses. A patient may have shown up for an initial or subsequent visit outside of the time period examined, have had an initial overdose in another state, or a patient may not have gone to the hospital at all due to use of a naloxone kit or perceived cost of services. These factors may have resulted in misclassification as a nonrepeat overdose. Additionally, if a patient did not disclose the drug on which they overdosed, and it was classified in the hospital as "unknown overdose", we may have incorrectly identified a patient's record as an overdose. Similarly, if a patient overdosed on more than one substance in a category, the patient may have been incorrectly classified as a non-polysubstance overdose. For the mental health comorbidities, we can only see what a patient decided to disclose in their first visit, what the health care provider put in the system, or what was not restricted by federal regulation (42 CFR Part 2). We did not have information on dosage of drugs used (for example benzodiazepines) or severity of the mental illness in this study. Additionally, the analysis did not include any residents who received care out of state due to unavailability of data. These patients may have had an initial visit or subsequent visits out of state that could not be accounted for. Both inpatients and outpatients showed nonproportional hazard rates, which may be a result of a confounding variable or time-dependent predictor. Last, it is possible that there are other variables that our investigation did not account for that could have affected the likelihood of repeat overdose.

5. Conclusion

We found evidence of the associations between polysubstance nonfatal overdose status and repeat overdose, regardless of initial visit type. Inpatients were more likely to return for another overdose event if the patient presented with a polysubstance overdose and one of those drugs was a benzodiazepine, which indicated that benzodiazepines play an important role in recurrent overdose. Inpatients were also more likely to return for an overdose event if they presented with a mental health disorder. These associations can help public health officials to develop guidelines and disseminate

information to providers and public health professionals about which patients are at risk for multiple overdose events. This may help to decrease the burden that repeat overdoses cause to the public and increase quality of life for all TN residents.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Appendix

Table A1. TN HDDS (2012-2016): ICD Codes used for identification of overdoses

Overdose Factors	Description	ICD-9-CM Codes	ICD-10-CM Codes†
All drug overdoses	Poisoning by drugs, medicaments, and biological substances	960-979, E850-E858, E950.0-E950.5, E962.0, E980.0-E980.5	T36-50
Non-heroin opioid overdose	Poisoning by opium	965.00	T40.0X
	Poisoning by methadone	965.02, E850.1	T40.3X
	Poisoning by other opioids		T40.2X
	Poisoning by synthetic narcotics	965.09, E850.2	T40.4X
	Poisoning by unspecified/other narcotics		T40.60, T40.69
Heroin overdose	Poisoning by heroin	965.01, E850.0	T40.1X
Benzodiazepine overdose	Poisoning by benzodiazepines	969.4, E853.2	T42.4X
Stimulant overdose	Poisoning by cocaine	970.81	T40.5X
	Poisoning by psychostimulants (excluding caffeine)	969.70, 969.72-969.79, E854.2	T43.60, T43.62-T43.69
Alcohol poisoning	Alcohol poisoning	980.0, E860.0, E860.1, E860.9	T51.0X, T51.9

† only intent codes 1-4 (accidental, intentional, assault, undetermined) and initial or missing encounter codes (not subsequent encounter or sequela)

Table A2. TN HDDS (2012-2016): ICD Codes used for identification of mental health comorbidities

Comorbidities	Description	ICD-9-CM Codes	ICD-10-CM Codes
Any mental health disorder	Any	290-319	F00-F99
Any mental health disorder (excluding drug/alcohol use)	Any	290, 293-302, 306-319	F01-F09, F20-F99
Depression	Major Depression	296.2-296.3, 298.0, 296.82, 311	F32.x, F33.x
	Bipolar Depression	296.5	F31.3-F31.5, F31.75-F31.76
	Adjustment disorder	309.0, 309.1, 309.28, 309.29, 309.3-309.4, 309.9	F43.2
Anxiety/post-traumatic stress disorder	Anxiety disorders	300.0, 300.2-300.3, 309.24, 309.28	F40.x-F42.x, F43.22-F43.23
	PTSD	309.81	F43.1
Schizophrenia, Psychosis, & Delusional disorders	Schizophrenia spectrum	295, 301.22	F20.x, F21.x, F25.x
	Psychosis and delusional disorders	297-298	F22.x- F24.x, F28.x-F29.x
Mood disorders	Manic episode	296.1, 296.81	F30.x
	Bipolar disorder (excluding depressive episodes)	296.0, 296.4, 296.6-296.7, 296.80, 296.89	F31.0-F31.2, F31.6, F31.70-F31.74, F31.77-F31.79, F31.8-F31.9
	Mood affective disorders (including dysthymia)	296.9, 300.4, 301.10, 301.12-301.13	F34.x-F39.x

underlined codes are included in more than one category due to multiple symptom types (e.g. 309.28, adjustment disorder with mixed anxiety & depressed mood)

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Tables

Table 1. TN HDDS (2012–2016): Factors by event type (single vs. multiple nonfatal overdose) for all drug overdoses – inpatient and outpatient.

Variable	Inpatient Visit for First Overdose (n = 21,066)		Outpatient Visit for First Overdose (n =36,244)	
	Single (n = 18,338) n (%)	Multiple (n = 2,728) n (%)	Single (n =31,198) n (%)	Multiple (n =5,046) n (%)
Age				
18-24 years	2,078 (11.3)	257 (9.4)	6,598 (21.2)	947 (18.8)
25-44 years	7,152 (39.0)	1,052 (38.6)	14,653 (47.0)	2,414 (47.8)
45-64 years	9,108 (49.7)	1,419 (52.0)	9,947 (31.9)	1,685 (33.4)
Race				
White	15,517 (84.6)	2,436 (89.3)	25,524 (81.8)	4,538 (89.9)
Non-white	2,821 (15.4)	292 (10.7)	5,674 (18.2)	508 (10.1)
Ethnicity				
Non-Hispanic	17,237 (99.0)	2,581 (99.4)	29,361 (98.8)	4,778 (99.2)
Hispanic	177 (1.0)	15 (0.6)	366 (1.2)	39 (0.8)
Sex				
Female	10,374 (56.6)	1,588 (58.2)	17,955 (57.6)	2,828 (56.0)
Male	7,964 (43.4)	1,140 (41.8)	13,240 (42.4)	2,218 (44.0)
Region (metropolitan area)				
Large	7,084 (38.6)	1,062 (38.9)	12,376 (39.7)	1,743 (34.5)
Medium	5,019 (27.4)	750 (27.5)	7,968 (25.4)	1,114 (22.1)
Small	2,026 (11.1)	283 (10.4)	2,544 (8.2)	333 (6.6)
Non-metropolitan	4,206 (22.9)	633 (23.2)	8,307 (26.6)	1,856 (36.8)
Payer				
Medicare	4,769 (26.0)	926 (33.9)	4,427 (14.2)	948 (18.8)
Medicaid	3,862 (21.1)	649 (23.8)	8,251 (26.5)	1,449 (28.7)
Commercial	3,951 (21.6)	410 (15.0)	8,093 (25.9)	1,012 (20.1)
Other Government	413 (2.3)	45 (1.7)	814 (2.6)	108 (2.1)
Cash/Self-Pay	4,810 (26.2)	616 (22.6)	8,754 (28.1)	1,385 (27.5)
Medically Indigent/Free	232 (1.3)	25 (0.9)	263 (0.8)	37 (0.7)
Other/unknown	301 (1.6)	57 (2.1)	596 (1.9)	107 (2.1)
Year of index overdose				
2012	4,306 (23.5)	763 (28.0)	6,766 (21.7)	1,212 (24.0)
2013	3,762 (20.5)	548 (20.1)	5,811 (18.6)	898 (17.8)
2014	3,367 (18.4)	463 (17.0)	5,887 (18.9)	913 (18.1)
2015	3,434 (18.7)	474 (17.4)	6,097 (19.5)	948 (18.8)
2016	3,469 (18.9)	480 (17.6)	6,637 (21.3)	1,075 (21.3)
Drugs present				
Benzodiazepines	4,604 (25.1)	766 (28.1)	5,548 (17.8)	1,025 (20.3)
Non-heroin Opioids	4,804 (26.2)	811 (29.7)	4,735 (15.2)	884 (17.5)
Heroin	416 (2.3)	86 (3.2)	1,604 (5.1)	431 (8.5)
Stimulants	1,929 (10.5)	231 (8.5)	1,737 (5.6)	229 (4.5)
Other drug	14,356 (78.3)	2,052 (75.2)	25,421 (81.5)	3,991 (79.1)
Alcohol poisoning	662 (3.6)	75 (2.8)	543 (1.7)	85 (1.7)
Polysubstance overdose - Yes	6,550 (35.7)	993 (36.4)	7,163 (23.0)	1,330 (26.4)
Drug categories present				
1	11,788 (64.3)	1,735 (63.6)	24,035 (77.0)	3,716 (73.6)
2	4,956 (27.0)	739 (27.1)	6,055 (19.4)	1,084 (21.5)
3	1,319 (7.2)	208 (7.6)	992 (3.2)	224 (4.4)
≥4	275 (1.5)	46 (1.7)	116 (0.4)	22 (0.4)
Mental Health				
Any Mental Health Disorder‡	11,060 (60.3)	1,836 (67.3)	12,586 (40.3)	2,013 (40.0)
Depression	6,824 (37.2)	1,047 (38.4)	8,210 (26.3)	1,270 (25.2)

Anxiety/Post-Traumatic Stress Disorder	4,439 (24.2)	792 (29.0)	4,394 (14.1)	651 (12.9)
Schizophrenia, Psychosis, & Delusional Disorders	1,067 (5.8)	208 (7.6)	1,060 (3.4)	220 (4.4)
Mood disorders	2,884 (15.7)	552 (20.2)	2,527 (8.1)	478 (9.5)

‡ Any Mental Health Disorder = depression, anxiety/PTSD, schizophrenia, mood disorders

Table 2. Adjusted Hazard Ratios (HRs) for repeat nonfatal overdose within first year following nonfatal overdose, HDDS 2012-2016

	Visit factors model		**Full model**	
	Inpatient Model (n = 21,066) HR (95% CI)	**Outpatient Model (n = 36,244) HR (95% CI)**	**Inpatient Model (n = 21,063) HR (95% CI)**	**Outpatient Model (n = 36,238) HR (95% CI)**
Benzodiazepine: present	0.98 (0.81, 1.20)	0.96 (0.84, 1.11)	0.95 (0.78, 1.16)	0.93 (0.81, 1.07)
Polysubstance: Yes	0.88* (0.78, 0.99)	1.09 (0.99, 1.20)	0.88* (0.78, 0.99)	1.08 (0.98, 1.18)
Benzodiazepine * Polysubstance interaction: Yes/Yes	1.29* (1.01, 1.63)	1.21* (1.01, 1.44)	1.29* (1.02, 1.64)	1.18 (0.99, 1.41)
Any MHD‡: Yes	1.31** (1.21, 1.42)	0.86** (0.80, 0.93)	1.28** (1.18, 1.39)	0.83** (0.77, 0.90)
Any MHD*time interaction	-	p < .0001	-	p < .0001
Age: 18-24	-	-	0.82** (0.72, 0.94)	0.94 (0.87, 1.02)
Age: 25-44	-	-	0.95 (0.87, 1.03)	1.01 (0.95, 1.07)
Race: Non-white	-	-	0.70** (0.62, 0.79)	0.57** (0.52, 0.63)
Sex: Male	-	-	1.15* (1.03, 1.30)	1.06 (1.00, 1.12)
Sex*time interaction	-	-	p < .01	-
Region: Large metropolitan area	-	-	1.07 (0.97, 1.18)	0.51** (0.46, 0.55)
Region: Medium metropolitan area	-	-	0.99 (0.89, 1.10)	0.53** (0.49, 0.57)
Region: Small metropolitan area	-	-	0.93 (0.81, 1.07)	0.56** (0.50, 0.63)
Region*time interaction	-	-	-	p < .0001

* = p <.05 ** = p < .01

‡: Any Mental Health Disorder, defined as presence of depression, anxiety/PTSD, schizophrenia, or mood disorder

Figure 1

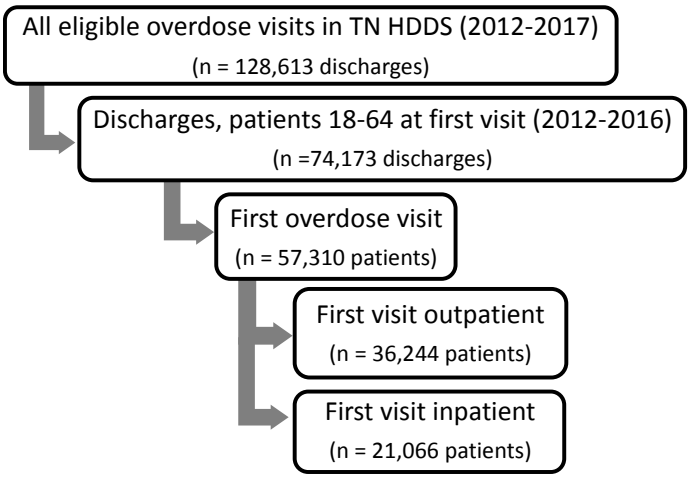


Fig. 1. Study sample derivation.

Figure 2

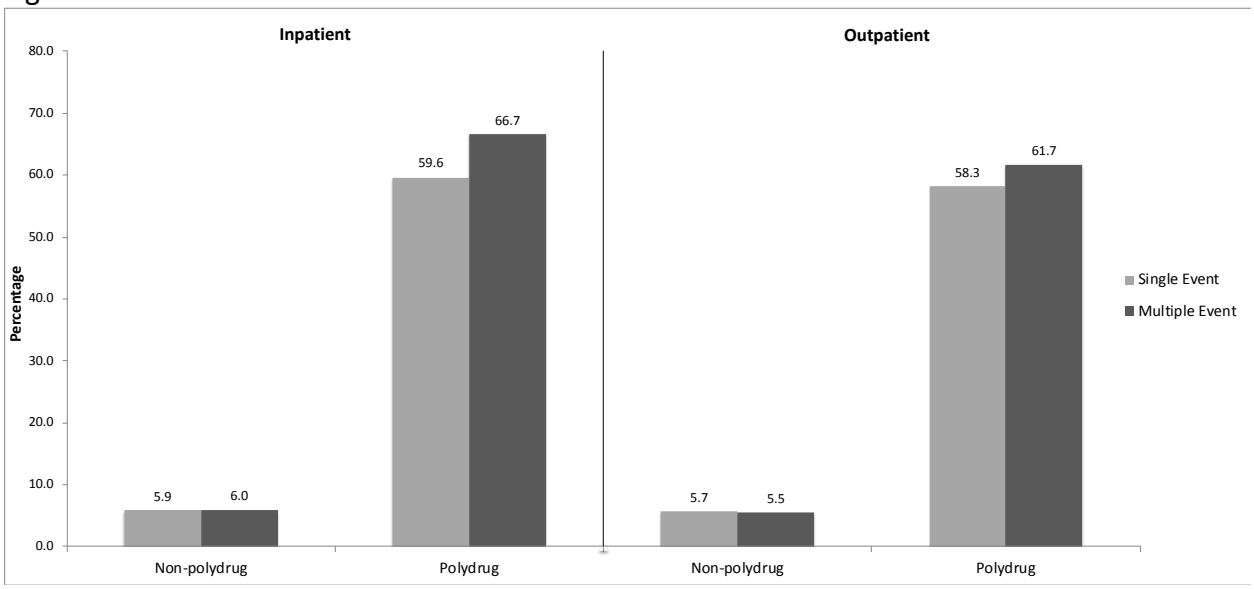


Fig. 2. Benzodiazepine involvement by polysubstance status.

Figure 3

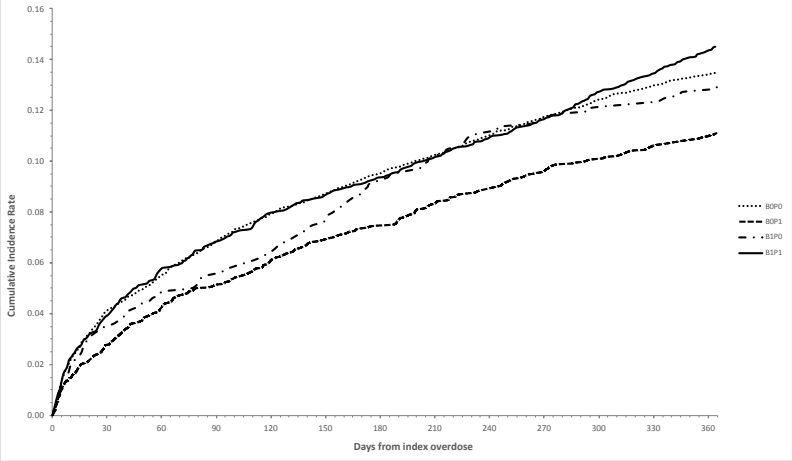
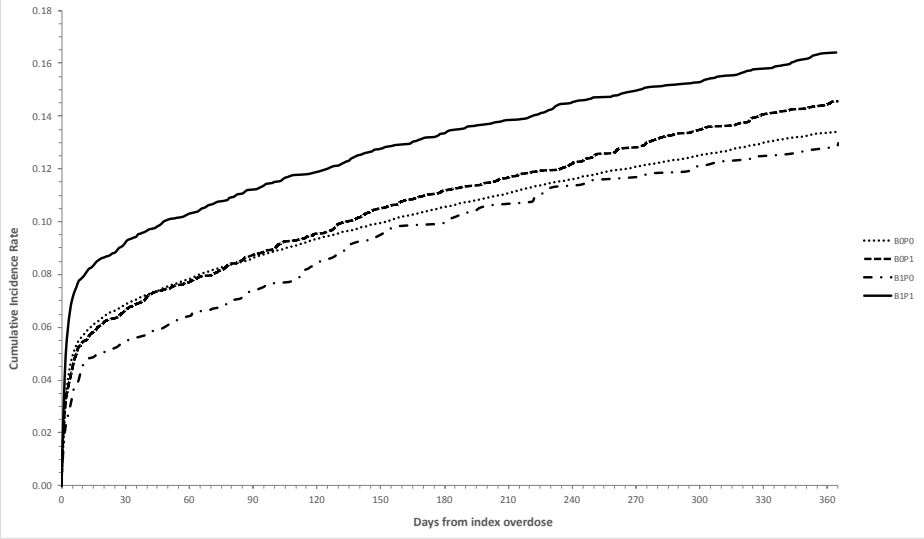


Fig. 3. TN HDDS (2012–2016): cumulative incidence rate of repeat overdose over time – **in**patients.

Figure 4



B0 – benzodiazepine absent
B1 – benzodiazepine present

P0 – non-polysubstance overdose
P1 – polysubstance overdose

Fig. 4. TN HDDS (2012–2016): cumulative incidence rate of repeat overdose over time – **ou**tpatients.