# Benzodiazepines increase the likelihood of both infectious and thrombotic complications

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**INTRODUCTION:** Benzodiazepines (BZDs) modulate peripheral γ-amino-butyric acid type A on macrophages causing immunomodulation. They inhibit proinflammatory cytokines increasing infections. Prior studies have also shown that infections can increase thrombotic complications. We sought to examine this relationship in trauma patients. We hypothesized that the presence of BZDs on admission urine drug screen (UDS) would increase rates of both complications.

**METHODS:** All patients submitted to the Pennsylvania Trauma Outcome Study database from 2003 to 2018 were queried. Those with a positive UDS for BZDs were analyzed. Infectious complications were defined as pneumonia, urinary tract infection, sepsis, wound, and soft tissue infection, and thrombotic complications were defined as presence of pulmonary embolism or deep vein thrombosis. Logistic regressions controlling for demographic and injury covariates assessed the adjusted impact of BZDs on infectious and thrombotic complications.

**RESULTS:** A total of 3,393 patients (2.08%) had infectious complications, and 3,048 (1.87%) had thrombotic complications. Furthermore, 33,260 patients (20.4%) had a positive UDS for BZDs on admission. Univariate analysis showed that those positive for BZDs had higher rates of infectious (3.33% vs. 1.76%, $p < 0.001$) and thrombotic (2.84% vs. 1.62%, $p < 0.001$) complications. Multivariate analysis revealed that BZDs significantly increased the odds of infectious and thrombotic complications. Patients who tested positive for BZDs and subsequently developed infection had increased odds (adjusted odds ratio, 1.65; $p < 0.001$) of developing thrombotic complications.

**CONCLUSION:** Trauma patients with a positive UDS for BZDs had higher odds of both infectious and thrombotic complications. Moreover, odds of thrombotic complications were higher in those with infections. (*J Trauma Acute Care Surg.* 2021;91: 206–211. Copyright © 2021 Wolters Kluwer Health, Inc. All rights reserved.)

**LEVEL OF EVIDENCE:** Epidemiological, level III.

**KEY WORDS:** Benzodiazepines; urine drug screen; complications; infection; thrombosis.

Benzodiazepines (BZDs) are a class of psychoactive drugs that are used to treat a range of disorders, such as anxiety, insomnia, agitation, seizures, and muscle spasms.[1] In the United States, 5.2% of adults aged 18 to 80 years took BZDs in 2008.[2] Multiple studies have demonstrated an association between BZD use and involvement in motor vehicle collisions.[3] In addition, long-acting BZDs like Valium have been associated with falls.[4,5] The prevalence and widespread use of these drugs in trauma patients beg the consideration of interactions during clinical treatment. Biologically, it is known that BZDs work by amplifying the effect of the neurotransmitter γ-amino-butyric acid (GABA) by allosterically modulating the GABA type A receptor expressed on immune cells.[6] There are multiple published studies that investigate the effect of BZD use on the immune system, but the conclusions are mixed.[7–10] Using mice as model organisms, Sanders et al.[7] found that mice were more likely to die from pneumonia when given BZDs. This suggests immunodeficiency effects of BZDs, since GABA is thought to decrease inflammatory responses of the immune system.[7] In human patients, Obiora et al.[8] found that BZDs may increase the likelihood of respiratory infection. They also found 30-day mortality to be 22% higher among patients taking BZDs. Their results were complemented by Nakafero et al.,[9] which used U.K. primary care data to demonstrate that patients taking BZDs have an increased likelihood of respiratory infection. On the contrary, other studies, namely, Dublin et al.,[10] suggest that BZDs do not increase the likelihood of respiratory infection. Despite the proposed immunomodulary mechanism of BZDs on the body, there is a scarcity of rigorous pharmacoepidemiologic research in human subjects to make a causal association.[11]

In regard to the effect BZDs have on thrombotic complications, multiple studies have shown increased thrombotic complications in those with BZD usage. Thomassen et al.[12] conducted a study that demonstrated that, out of the psychotropic drugs analyzed (antipsychotics, antidepressants, and BZDs), BZDs had the highest odds ratio of developing deep vein thrombosis (DVT). In addition, it has been shown that BZD receptor agonists significantly increase odds of venous thromboembolism (VTE), with BZD hypnotics having higher odds of VTE.[13]

Our study sought to add to the existing literature on immunosuppressive effects and thrombotic complications of BZDs, as it relates to trauma patients. Specifically, we sought to determine if rates of infectious or thrombotic complications among trauma patients were higher in those who tested positive for BZDs on

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admission. We hypothesized, because of its interaction with the immune system, the presence of BZDs would be associated with higher rates of infectious and thrombotic complications.

## PATIENTS AND METHODS

Following review and approval by the Institutional Review Board at Penn Medicine Lancaster General Health, the Pennsylvania Trauma Outcome Study (PTOS) database was retrospectively queried for trauma admissions of all ages from 2003 to 2018 who had a urine drug screen (UDS) on admission. Pennsylvania Trauma Outcome Study is a database that contains statewide trauma registry data for all hospitals accredited by the Pennsylvania Trauma System Foundation. Trauma patients included within the database met at least one of the following inclusion criteria: death secondary to trauma, intensive care unit (ICU)/step-down unit admissions, hospital stay >48 hours or hospital stay between 36 and 48 hours with Injury Severity Score of >9, or admitted transfers in and/or out of the hospital. Since its establishment in 1984 as part of the Emergency Medical Services Act, Pennsylvania Trauma System Foundation has served as the accrediting body for all trauma centers in the state of Pennsylvania. Pennsylvania Trauma System Foundation accredits adult and pediatric centers alike, in accordance with the American College of Surgeon standards set forth in the Resources for Optimal Care of the Injured Patient.[14]

All patients presenting to an accredited PA trauma center from 2003 to 2018 who had a UDS on admission were queried. Those presenting dead on arrival were excluded. Because of the small sample size, patients presenting with skin disease as their primary mechanism of injury were also excluded. Patients who had a positive UDS for BZDs on admission met the inclusion criteria. Within this subset, infectious and thrombotic complications were analyzed (Fig. 1). Infectious complications were defined as a hospital complication of pneumonia, urinary tract infection, sepsis, wound, or soft tissue infection. Thrombotic complications were defined as the presence of pulmonary embolism or DVT. Variables of interest included positive UDS for BZDs upon admission, patient demographics (age, sex), injury classification (injury type, Injury Severity Score), Glasgow Coma Scale (GCS), admission systolic blood pressure (SBP), head Abbreviated Injury Scale (AIS), infectious complications, thrombotic complications, length of stay (hospital and ICU), ventilator days, and mortality.

Univariate analysis in the form of two-sample *t* tests and $\chi^2$ were used to assess unadjusted baseline demographics, injury patterns, and outcome differences in those who had +UDS for BZDs versus those who did not. Logistic regressions controlling for age, sex, injury severity, injury type, admission GCS and SBP, head AIS score of ≥3, and ventilator days assessed the adjusted impact of the presence of BZDs on infectious and thrombotic complications. An additional logistic regression controlling for age, sex, injury severity, injury type, admission GCS and SBP, head AIS score of ≥3, and ventilator days was used to assess the development of thrombotic complications in those who tested positive for BZDs and subsequently developed an infectious complication. All data manipulation and statistical analyses were performed using Stata/IC (version 16.0; Stata Corp, College Station, TX). Statistical significance was defined as a *p* value of <0.05. The area under the receiver operating characteristic was calculated as a performance measure for the multilevel regression model.

## RESULTS

Of patients who had UDS on admission, 33,260 patients (20.4%) had a positive UDS for BZDs (Fig. 1). When analyzing the percent of positive UDS for BZDs over the study period, a bell curve is seen with the lowest percent positive being present in 2003 (15.6% positive) and 2018 (15.3% positive) and the

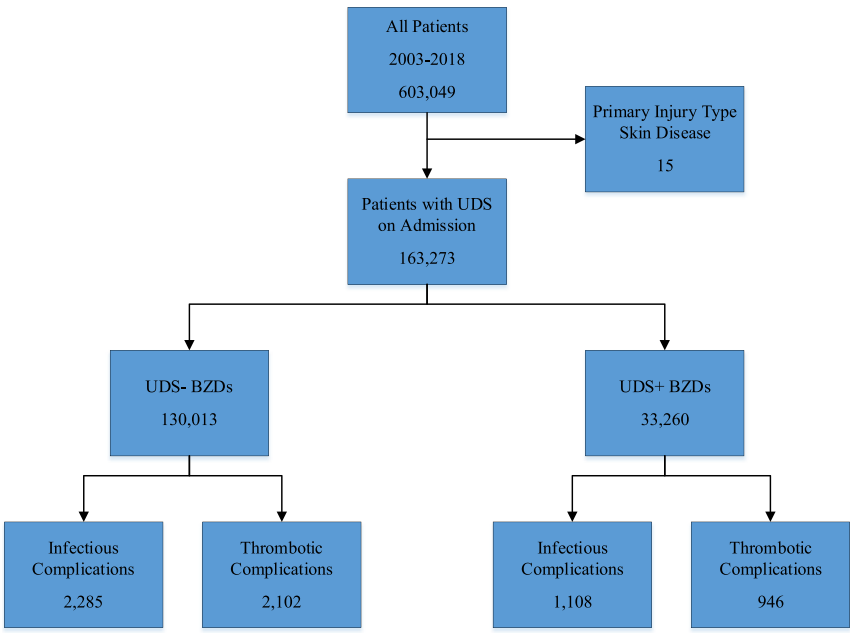


**Figure 1.** Study inclusion criteria.

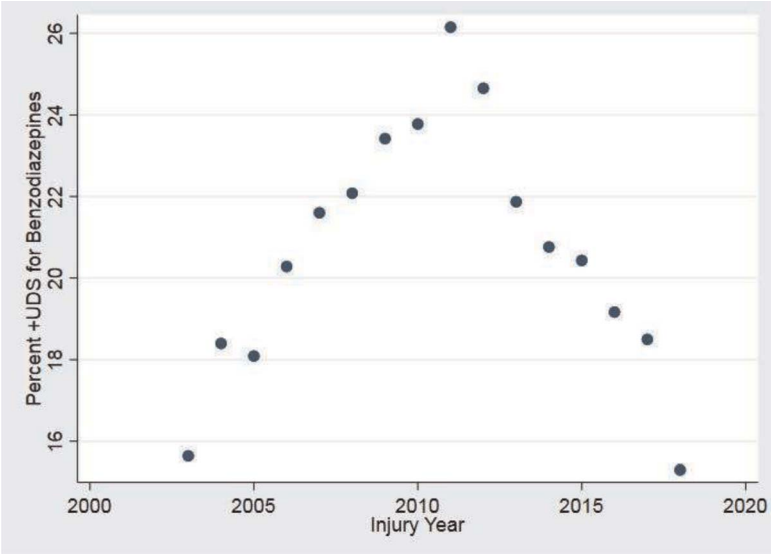


**Figure 2.** Percentage of positive UDS for BZDs over study period (2003–2018).

highest percent positive occurring in 2011 with 26.2% of UDS being positive for BZDs (Fig. 2). Univariate analysis revealed that those who tested positive for BZDs were more likely to be male (69.9% vs. 66.6%, $p < 0.001$), younger (mean age, 41.7 years vs. 48.3 years; $p < 0.001$), and have a penetrating mechanism of injury (13.8% vs. 8.0%, $p < 0.001$) compared with those who tested negative for BZDs. Patients positive for BZDs were more likely to have a head AIS score of ≥3 (53.0% vs. 46.9%; $p < 0.001$). Those positive for BZDs on admission spent, on average, more time in the hospital (8.22 days vs. 5.82 days, $p < 0.001$), in the ICU (3.81 days vs. 1.97 days, $p < 0.001$), and on the ventilator (2.47 days vs. 0.99 days, $p < 0.001$). Mortality was slightly higher in those who had +UDS for BZDs (5.68% vs. 4.51%, $p < 0.001$). Injury Severity Score, GCS, and SBP were similar between groups (Table 1).

When looking at all patients who had UDS on admission, 3,393 patients (2.08%) had infectious complications, and 3,048 (1.87%) had thrombotic complications. Univariate analysis showed that those positive for BZDs had higher rates of infectious (3.33% vs. 1.76%, $p < 0.001$) and thrombotic (2.84% vs. 1.62%, $p < 0.001$) complications compared with those who had a −UDS for BZDs. Within the complications grouped as infectious, the +UDS for BZDs group had a higher of percentage of patients who developed pneumonia (0.42% vs. 0.23%, $p < 0.001$), wound infection (1.23% vs. 0.59%, $p < 0.001$), soft tissue infection (0.46% vs. 0.24%, $p < 0.001$), and sepsis (1.38% vs. 0.70%, $p < 0.001$). There was no difference between +/−UDS for the percentage of patients who developed urinary tract infection (0.20% vs. 0.18%, $p = 0.541$). Within the thrombotic complications, the patients positive for BZDs had higher percentages of patients who developed DVT (2.22% vs. 1.23%, $p < 0.001$) and pulmonary embolism (0.82% vs. 0.49%, $p < 0.001$) (Table 1).

Multivariate analysis revealed that BZDs significantly increased the odds of infectious (adjusted odds ratio [AOR], 1.27; 95% confidence interval [CI], 1.17–1.38; $p < 0.001$) and thrombotic complications (AOR, 1.21; 95% CI, 1.11–1.32; $p < 0.001$) (Table 2). Within infectious complications, the presence of BZDs on admission significantly increased the odds of pneumonia (AOR, 1.32; $p = 0.013$), wound infection (AOR, 1.43; $p < 0.001$), soft tissue infection (AOR, 1.33; $p = 0.006$), and sepsis (AOR, 1.22; $p = 0.003$). The presence of BZDs did not increase the odds of urinary tract infection development (AOR, 1.13; $p = 0.406$). Of the complications included in the thrombotic variable, BZDs increased the odds of the development of DVT (AOR, 1.18; $p = 0.001$) and pulmonary embolism (AOR, 1.30; $p = 0.001$) (Table 3). Patients who tested positive for BZDs and subsequently developed infection had increased odds (AOR, 1.65; 95% CI, 1.27–2.12; $p < 0.001$) of developing thrombotic complications (Table 4).

## DISCUSSION

The results of our study demonstrate an association between the use of BZDs in trauma patients and an increase in both infectious and thrombotic complications. A positive UDS at admission was associated with increased odds of both infectious (AOR, 1.27; $p < 0.001$) and thrombotic complications (AOR, 1.21; $p < 0.001$). Moreover, those who developed an infection with a positive UDS had increased odds of developing a concurrent thrombotic complication (AOR, 1.65; $p < 0.001$).

While the exact mechanisms of how BZDs modulate infectious and thrombotic responses are unknown, it is well documented that their presence in trauma affects clinical outcomes. Cheng et al.[15] most recently demonstrated that the presence of BZDs in trauma patients increases the need for operative intervention, the length of ICU admission, and the need for mechanical ventilation. Our study supports several of their findings with demonstrable increases in ICU length of stay (3.81 ± 8.08 days, $p < 0.001$), hospital length of stay (8.22 ± 11.2 days, $p < 0.001$), ventilator days (2.47 ± 6.52 days, $p < 0.001$), and all-cause mortality (5.68%, $p < 0.001$). Increased rates of infection with BZD use, particularly pneumonia, are also well documented in the literature and further supported by the results of our study (AOR, 1.32; $p = 0.013$).[8,15] The effect of BZD use on these outcomes may be

**TABLE 1.** Univariate analysis of patients with a positive UDS for BZDs versus patients with a negative UDS for BZDs from the PTOS database

| | Patients with +UDS for BZDs (n = 33,260) | Patients with −UDS for BZDs (n = 130,013) | *p* |
|---|---|---|---|
| Sex | | | |
| Male, n (%) | 23,255 (69.9) | 86,537 (66.6) | <0.001 |
| Age, y | | | |
| Mean (SD) | 41.7 (18.6) | 48.3 (22.9) | <0.001 |
| Mechanism of injury, n (%) | | | |
| Blunt | 27,305 (82.1) | 116,720 (89.8) | <0.001 |
| Penetrating | 4,578 (13.8) | 10,425 (8.0) | |
| Burn | 1,373 (4.1) | 2,835 (2.2) | |
| ISS | | | |
| Median (IQR) | 10 (5–21) | 10 (5–17) | <0.001 |
| GCS | | | |
| Median (IQR) | 15 (7–15) | 15 (15–15) | <0.001 |
| SBP, mm Hg | | | |
| Mean (SD) | 135.2 (29.9) | 139.0 (29.6) | <0.001 |
| Head AIS ≥3, n (%) | 9,488 (53.0) | 31,525 (46.9) | <0.001 |
| Infectious complications (total), n (%) | 1,108 (3.33) | 2,285 (1.76) | <0.001 |
| Pneumonia | 140 (0.42) | 302 (0.23) | <0.001 |
| UTI | 66 (0.20) | 237 (0.18) | <0.001 |
| Wound infection | 408 (1.23) | 773 (0.59) | 0.541 |
| Soft tissue infection | 154 (0.46) | 310 (0.24) | <0.001 |
| Sepsis | 458 (1.38) | 912 (0.70) | <0.001 |
| Thrombotic complications (total), n (%) | 946 (2.84) | 2,102 (1.62) | <0.001 |
| DVT | 737 (2.22) | 1,602 (1.23) | <0.001 |
| PE | 272 (0.82) | 643 (0.49) | <0.001 |
| ICU LOS, d | | | |
| Mean (SD) | 3.81 (8.08) | 1.97 (5.52) | <0.001 |
| Hospital LOS, d | | | |
| Mean (SD) | 8.22 (11.2) | 5.82 (8.23) | <0.001 |
| Ventilator days | | | |
| Mean (SD) | 2.47 (6.52) | 0.99 (4.45) | <0.001 |
| Mortality, n (%) | 1,888 (5.68) | 5,866 (4.51) | <0.001 |

IQR, interquartile range; ISS, Injury Severity Score; LOS, length of stay; PE, pulmonary embolism; UTI, urinary tract infection.

due to their known impairment or delay of physiologically protective mechanisms (i.e., cough/gag reflexes, responses to noxious stimuli) and role in immunosuppression at a cellular level.[16–18]

Our finding of the association of increased thrombotic events in trauma patients with a positive UDS and infection is of particular interest. Kaplan et al.[19] demonstrated that, among critically ill patients, the presence of sepsis and septic shock increased the rate of VTE. They posited that, while the exact mechanism was unclear, this increase in VTE may be related to an imbalance between conflicting prothrombotic and antithrombotic mediators in the setting of infection and sepsis, pharmacologic modulation, physical immobility after major injury, or a yet undiscovered peripheral mechanism. Our study supports similar findings in trauma patients. We have demonstrated that the presence of BZDs alone is associated with increased odds of VTE (AOR, 1.21; $p < 0.001$) with the presence of a concomitant infection significantly increasing those odds (AOR, 1.65; $p < 0.001$). While cellular-level studies would lead one to anticipate that BZD use should lead to coagulopathy and lower VTE,[20,21] our study reiterates that their use is part of the complex traumatic, pharmacologic, and immunologic modulation that leads to the mixed phenotypic presentation of trauma-induced coagulopathy.[22,23]

**TABLE 2.** Multivariate analysis of the presence of BZDs on infectious and thrombotic complications

| | Infectious Complications | | Thrombotic Complications | |
|---|---|---|---|---|
| **Variable** | **AOR (95% CI)** | ***p*** | **AOR (95% CI)** | ***p*** |
| +UDS for BZDs | 1.27 (1.17–1.38) | <0.001 | 1.21 (1.11–1.32) | <0.001 |
| Age | 1.01 (1.01–1.01) | <0.001 | 1.01 (1.00–1.01) | <0.001 |
| Male sex | 1.18 (1.09–1.29) | <0.001 | 1.32 (1.20–1.44) | <0.001 |
| ISS | | | | |
| Mild: 0–9 | Reference | — | Reference | — |
| Moderate: 10–16 | 1.86 (1.65–2.09) | <0.001 | 2.32 (2.04–2.63) | <0.001 |
| Severe: 17–25 | 2.89 (2.58–3.23) | <0.001 | 4.03 (3.56–4.55) | <0.001 |
| Profound: 26–75 | 3.95 (3.51–4.45) | <0.001 | 5.94 (5.23–6.74) | <0.001 |
| GCS | | | | |
| 15 | Reference | — | Reference | — |
| >15 | 1.01 (0.93–1.10) | 0.781 | 1.09 (1.00–1.19) | 0.045 |
| Admission SBP, mm Hg | | | | |
| Hypo: <80 | 0.96 (0.79–1.15) | 0.634 | 0.93 (0.77–1.14) | 0.499 |
| Normal: 80–119 | Reference | — | Reference | — |
| Prehyper: 120–139 | 0.73 (0.65–0.80) | <0.001 | 0.80 (0.72–0.89) | <0.001 |
| Hyper: ≥140 | 0.71 (0.65–0.78) | <0.001 | 0.74 (0.67–0.81) | <0.001 |
| Injury type | | | | |
| Blunt | Reference | — | Reference | — |
| Penetrating | 2.14 (1.92–2.40) | <0.001 | 1.30 (1.15–1.48) | <0.001 |
| Burn | 2.24 (1.88–2.68) | <0.001 | 0.51 (0.39–0.69) | <0.001 |
| Head AIS ≥3 | 1.02 (0.93–1.12) | 0.692 | 1.12 (1.01–1.23) | 0.034 |
| Ventilator days | 1.10 (1.10–1.11) | <0.001 | 1.08 (1.07–1.08) | <0.001 |
| | AUROC: 0.8302 | | AUROC: 0.8134 | |

AUROC, area under the receiving operating characteristic; ISS, Injury Severity Score.

**TABLE 3.** Multivariate analysis of the presence of BZDs and development of specific infectious and thrombotic complications

| **Complication** | **AOR (95% CI)** | ***p*** | **AUROC** |
|---|---|---|---|
| Infectious | | | |
| Pneumonia | 1.32 (1.06–1.63) | 0.013 | 0.8319 |
| UTI | 1.13 (0.85–1.51) | 0.406 | 0.7884 |
| Wound infection | 1.43 (1.26–1.63) | <0.001 | 0.8043 |
| Soft tissue infection | 1.33 (1.08–1.64) | 0.006 | 0.7777 |
| Sepsis | 1.22 (1.07–1.38) | 0.003 | 0.8981 |
| Thrombotic | | | |
| DVT | 1.18 (1.07–1.30) | 0.001 | 0.8327 |
| PE | 1.30 (1.12–1.51) | 0.001 | 0.7617 |

*Adjusted for age, sex, injury severity, injury type, admission GCS, SBP, head AIS ≥3, and ventilator days.

AUROC, area under the receiving operating characteristic; PE, pulmonary embolism; UTI, urinary tract infection.

**TABLE 4.** Multivariate analysis of the presence of BZDs and development of infection on thrombotic complications

| | Thrombotic Complications | |
|---|---|---|
| **Variable** | **AOR (95% CI)** | ***p*** |
| +UDS for BZDs and subsequent infection | 1.65 (1.27–2.12) | <0.001 |
| Age | 1.00 (1.00–1.01) | <0.001 |
| Male sex | 1.29 (1.15–1.44) | <0.001 |
| ISS | | |
| Mild: 0–9 | Reference | — |
| Moderate: 10–16 | 4.08 (3.16–5.27) | <0.001 |
| Severe: 17–25 | 7.72 (6.05–9.84) | <0.001 |
| Profound: 26–75 | 12.7 (9.87–16.2) | <0.001 |
| GCS | | |
| 15 | Reference | — |
| >15 | 1.24 (1.11–1.39) | <0.001 |
| Admission SBP, mm Hg | | |
| Hypo: <80 | 0.83 (0.63–1.10) | 0.192 |
| Normal: 80–119 | Reference | — |
| Prehyper: 120–139 | 0.86 (0.75–0.99) | 0.030 |
| Hyper: ≥140 | 0.79 (0.69–0.89) | <0.001 |
| Injury type | | |
| Blunt | Reference | — |
| Penetrating | 0.94 (0.74–1.21) | 0.655 |
| Burn | 0.29 (0.08–1.03) | 0.055 |
| Head AIS ≥3 | 0.79 (0.70–0.89) | <0.001 |
| Ventilator days | 1.09 (1.08–1.09) | <0.001 |
| | AUROC: 0.8561 | |

AUROC, area under the receiving operating characteristic; ISS, Injury Severity Score.

Because this study was retrospective and only used data from the PTOS database, these findings will need to be replicated in the greater trauma population. Moreover, we were limited by the data provided in the database, which can be incomplete, incorrect, or limited based on the options presented for entry. As with all large database studies, there are several inherent biases that affect the greater application of our findings to direct clinical practice. Being a trauma registry also limits the data to those admitted to an accredited trauma center, excluding those who were not taken to a trauma center. Because PTOS is a large database, some variables may contain missing data such as the variable for UDS. To adjust for this, only patients who had a UDS recorded were included, opening the study up to bias. The self-reporting of infection and VTE presents further risk of confounding, as each participant's method of diagnosis (i.e., culture, screening ultrasound, and clinical presentation) is not noted in PTOS. The usage and duration of concurrent prophylactic antibiotics and anticoagulation are also not captured by PTOS.

Of note, our utilization of the UDS as a surrogate for the presence of BZD use on admission presents some confounding risks. The UDS was chosen as this study's screening tool as opposed to the criterion standard of mass spectrometry for both practical and economic reasons, although this opens it to several areas of bias. While not as definitive as mass spectrometry for identification of BZD usage, urine drug screening is a reliable, expedient, and fiscally sound for most trauma providers.[24] False-positive results have been reported with the selective serotonin reuptake inhibitor sertraline[25] and the non-steroidal anti-inflammatory drug oxaprozin,[26] but the UDS retains a valuable tool for screening for drug usage.

Finally, the very nature of a qualitative UDS may also play a role in the results of this study. We recognize that the standard UDS is typically drawn after initial resuscitation efforts and is unable to distinguish between either prehospital use or administration within the process of ATLS and initial injury management. We decided to include all patients in our study with a positive UDS, as it is difficult to determine this timing using only a database. This oversimplification adds some bias, as it obfuscates the timing of prehospital use and clinical necessity such as in intubation or sedation for combativeness. Moreover, although BZDs exhibit a dose effect, this too is difficult to determine using only a database and is only measureable using mass spectrometry or send out studies, which are rarely used in day-to-day practice. Fortunately, these assumptions reflect the typical trauma provider who may not be able to distinguish the temporal exposure or know the total dosing the patient in a practical setting often relying upon a positive UDS alone to direct clinical treatment. On a different note, while we used UDS on admission as our surrogate, we were unable to account for those patients who received BZDs while in the hospital and how this subsequently affected the rates of infectious and thrombotic complications.

## CONCLUSION

Trauma patients who had a positive UDS for BZDs on admission had higher odds of associated infectious and thrombotic complications. In addition, the odds of thrombotic complications were significantly higher in those patients with a positive UDS and a concurrent infection. Further study will be needed to replicate our findings by extending this analysis to include larger databases (i.e., National Trauma Data Bank), and targeted subanalyses of specific vulnerable populations (i.e., intubated and traumatic brain injury patients) will be needed to better control for some of the confounding factors.

### AUTHORSHIP

E.S. contributed in the study design, interpretation of data, and article preparation. M.M. contributed in the data collection, data analysis, interpretation of data, and article preparation.
C.B. contributed in the article preparation and literature review. E.B. contributed in the study design, interpretation of data, and editorial oversight. F.R. contributed in the study design, interpretation of data, and editorial oversight.

### DISCLOSURE

The authors declare no conflicts of interest.
The opinions and views expressed in this article are solely those of the author(s) and do not represent an endorsement by or position of the Pennsylvania Trauma Systems Foundation

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