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The impact of pre-injury controlled substance use on clinical outcomes following trauma

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Abstract

Background—A disproportionately high percentage of trauma patients use controlled substances, and they often co-ingest multiple drugs. Previous studies have evaluated the effect of individual drugs on clinical outcomes following trauma. However, the impact of all drugs included in a comprehensive screening panel has not yet been compared in a single cohort of patients.

Methods—All trauma patients who underwent urine drug screens following admission to the LAC+USC Medical Center (01/2008-06/2015) were identified retrospectively. Univariable and multivariable regression analyses determined the significance of all drugs tested in the hospital's standard toxicology screen (amphetamine, barbiturate, benzodiazepine, cocaine, opiate, phencyclidine) on clinical outcomes.

Results—A total of 10,288 patients who underwent admission toxicology screening were identified. While 5,661 patients had completely negative screens, 3,370 patients tested positive for

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Author Contribution
All authors contributed to the design of this study. V.C., M.J., K.I., and D.D. conducted the literature search and collected data. V.C., M.J., S.B., Y.J., K.I., and D.D. performed data analysis. V.C., S.B., Y.J., K.M., T.H., E.B., L.L., K.I., and D.D. contributed to data interpretation. All authors participated in writing the manuscript. V.C., S.B., Y.J., K.M., T.H., E.B., L.L., K.I., and D.D. contributed to critical revision.

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only one drug and 1,257 patients tested for multiple drugs. Univariable analysis indicated that patients who tested positive for multiple drugs had higher rates of operative intervention ($p<0.001$), longer hospital stay ($p<0.001$), and longer ICU stays ($p<0.001$). Multivariable analysis indicated that phencyclidine was associated with higher rates of mortality ($p=0.028$) while amphetamine was associated with lower rates of mortality ($p=0.008$). Higher rates of operative intervention were observed in patients testing positive for amphetamine ($p<0.001$), benzodiazepine ($p<0.001$), or opiate ($p<0.001$). Benzodiazepine use was associated with higher rates of mechanical ventilation ($p<0.001$), but use of amphetamines ($p=0.030$) or opiates ($p<0.001$) was associated with lower rates.

Conclusions—Pre-injury use of amphetamine, barbiturate, benzodiazepine, cocaine, opiate, and PCP have significant and variable impact on clinical outcomes following trauma. Comparing the relative effect of each drug class can help clinicians risk-stratify all trauma patients, including those who test positive for multiple substances.

Keywords

Trauma; Outcomes; Toxicology; Controlled Substance

Background

Controlled substance use has dramatically escalated in the last two decades. Between 1999 and 2002, US prescriptions for oxycodone, morphine, and fentanyl increased by 50%, 60%, and 150%, respectively (1-3). Likewise, amphetamine prescriptions doubled between 1994 and 2004 (4). More recently from 2007 to 2011, total US opiate, benzodiazepine, and amphetamine prescriptions grew 17%, 16%, and 39% (5). The increasing number of controlled substance prescriptions reflects not only the amplified use by existing patients but also an expanding population of users (6, 7). In particular, misuse and abuse of both prescription and illegal drugs have increased 13% (8). Consequently, healthcare providers must care for an increasing number of patients illicitly using controlled substances.

Controlled substance use is especially prominent in patients admitted for traumatic injury (3, 9). In response to the growing prevalence of drug use, investigators have examined the relationship between pre-injury use of amphetamine (10-14), benzodiazepine (15), cocaine (16-21), and opiate (22) with injury patterns and clinical outcomes. However, even within a single drug class, studies have reported conflicting relationships between pre-injury controlled substance use and mortality, operative intervention, mechanical ventilation, hospital length of stay (LOS), and intensive care unit (ICU) LOS.

To further obscure the characterization of clinical outcomes in patients who use drugs, illicit drug use frequently involves concurrent use of multiple substances. Previous studies have focused on one drug, often inconsistently accounting for patients testing positive for a variety of drugs. In fact, these studies often excluded patients testing positive for alcohol, one of the most common co-ingestants (10, 22, 23). The authors of the present study hypothesize that the clinical outcomes following traumatic injury of patients who test positive for a controlled substance differ significantly not only from those of patients who test negative for all controlled substances, but also from the outcomes of patients who test

positive for other controlled substances. Therefore, the purpose of the present study was to evaluate the impact of amphetamine, barbiturate, benzodiazepine, cocaine, opiate, and phencyclidine (PCP) on clinical outcomes following trauma. By comprehensively incorporating all results of admission urine toxicology screening, this study aims to compare the relative impact of each controlled substance. Furthermore, the study also assesses the impact of concurrent alcohol use on the association between pre-injury controlled substance use and clinical outcomes.

Methods

Patient Selection

The Institutional Review Board of the University of Southern California Health Sciences Campus approved this project. This single-center, retrospective observational study included all trauma patients 13 years and older who were admitted to the LAC+USC Medical Center between January 1, 2008, and July 31, 2015. All trauma patients who underwent an admission urine toxicology screen were included. Routine urine toxicology panels tested for the presence of amphetamine, barbiturate, benzodiazepine, cocaine, opiate, and PCP without quantification. Although quantified drug levels were reported in a few unique cases, routine urine toxicology screens report only a binary result, positive or negative, depending on whether a threshold urine concentration is met. To reflect this clinical practice, the present study analyzes controlled substance use as a binary variable. Admission blood alcohol level (BAL) data were extracted and maintained as a continuous variable because this data were primarily reported as a continuous level for clinicians.

Additionally, patient characteristics including age, sex, admission systolic blood pressure (SBP), admission Glasgow Coma Score (GCS), Injury Severity Score (ISS), Abbreviated Injury Scale (AIS) by body part, and mechanism of injury were also collected. Mechanism of injury was categorized as penetrating, blunt, other (e.g., burn), or a combination of the three. Clinical outcome variables included mortality, operative intervention, mechanical ventilation, ICU admission, hospital LOS, and ICU LOS.

Statistical Analysis

The significance of pre-injury controlled substance use on outcome variables was determined using both univariate and multivariate regression analyses. In univariate analysis, patients were stratified into eight mutually exclusive groups determined by urine toxicology screening results: completely negative, amphetamine-positive only, barbiturate-positive only, benzodiazepine-positive only, cocaine-positive only, opiate-positive only, PCP-positive only, and poly-drug-positive. The chi-square test of independence with post hoc Bonferroni correction ($\alpha = 0.05$) was used to examine associations between drug group and dichotomous outcome variables (mortality, operative intervention, mechanical ventilation, and ICU admission). One-way analysis of variance (ANOVA) with post hoc Bonferroni correction ($\alpha = 0.05$) was used to examine associations between drug group and continuous outcome variables (ICU LOS and hospital LOS).

Multivariable analysis adjusted for differences in patient characteristics including age, sex, admission SBP, admission GCS, ISS, and mechanism of injury. GCS was used in lieu of AIS for three reasons. First, GCS is a more objective measurement than AIS. Second, GCS has been consistently used in previous literature assessing controlled substances in trauma patients (10, 16, 18, 19). Third, GCS has been validated as an appropriate indicator of traumatic brain injury despite intoxication in trauma patients (24).

For multivariate analysis, urine drug screen results for each controlled substance were characterized as binary variables (i.e., positive or negative). The main effects of controlled substances were simultaneously included in logistic and linear regression models to assess their significance as predictors of dichotomous and continuous outcome variables, respectively. Before linear regression analysis, satisfaction of all statistical assumptions necessary for linear regression was confirmed. This entailed transforming hospital LOS and ICU LOS via base 10 logarithmic ($\log_{10}$) transformation. Regression model performance were also tested. For logistic regression, calibration and discrimination were examined with the Hosmer and Lemeshow Test and area under the receiver operating characteristic (ROC) curve. For linear regression, R^2 coefficients were examined.

Pairwise interactions were also examined in multivariate analysis adjusting for differences in patient characteristics. This was performed to determine whether use of each substance remained significant in the presence of others, and to assess any synergistic or antagonistic effects of combination drug use.

Data were managed and analyzed using SPSS version 23 (IBM Corporation, Armonk, NY).

Subgroup Analysis

Subgroup analysis was conducted for patients who underwent admission blood alcohol screening. BAL data were maintained as a continuous variable. The multivariate analyses of each controlled substance controlling for patient characteristics were repeated with blood alcohol level included as a continuous independent predictor of clinical outcomes.

Results

During the study timeframe, 10,166 patients satisfied inclusion criteria (Figure 1). Patient age ranged from 13 to 103 years (mean 39.2; standard deviation [SD] 16.8). Of all patients, 8,076 (79.3%) were male. The median ISS and GCS at admission were 5.0 (interquartile range [IQR] 2.0-13.0) and 15.0 (IQR 14.0-15.0), respectively. Overall, 8,465 (83.3%) and 1,735 (17.1%) patients were admitted for blunt and penetrating injuries respectively; 18 (0.2%) sustained other types of injuries (e.g., burn, electrical shock; Table 1). The most common mechanisms of injury were motor vehicle collision (2,581 patients, 25.3%), falls (2,507 patients, 24.7%), pedestrian or bicyclist thrown or run over (1,520 patients, 15.0%), assault (861 patients, 8.5%), and stabbing (824 patients, 8.1%; Table 2).

Of all patients, 5,621 patients (55.3%) had completely negative urine toxicology screens and 4,545 patients (44.7%) tested positive for at least one controlled substance. Of the patients who had positive urine toxicology screens, opiate was the most frequently used controlled

substance (2,268 patients, 49.9%), followed by amphetamine (1,393 patients, 30.6%), benzodiazepine (1,085 patients, 23.9%), cocaine (1,019 patients, 22.4%), PCP (130 patients, 2.9%), and barbiturate (126 patients, 2.8%). Furthermore, 3,292 patients (72.4%) tested positive for only one drug class while 1,253 patients (27.6%) tested positive for multiple controlled substances. Of patients in the former group, 754 patients (22.9%) used amphetamine, 63 patients (1.9%) barbiturate, 501 patients (15.2%) benzodiazepine, 553 patients (16.8%) cocaine, 1,368 patients (41.6%) opiate, and 53 patients (1.6%) PCP. Of all patients, 5,987 patients underwent BAL testing (Figure 1). Positive alcohol screens were identified in 3,276 patients (54.7%).

Univariate analysis indicated a significant difference in all clinical outcomes assessed across all drug categories (Table 3). Even after adjusting for age, sex, admission SBP, admission GCS, ISS, and mechanism of injury in multivariate analysis, pre-injury controlled substance use was a significant predictor of all clinical outcomes (Table 4). Characterization of each controlled substance as a risk or protective factor varied across dichotomous outcomes. All controlled substances were associated with prolonged hospital LOS and ICU LOS. In subgroup analysis, BAL did not represent a significant predictor for any clinical outcome tested.

The Hosmer and Lemeshow Test statistics for logistic model calibration were χ^2 (with 8 degrees of freedom [d.f.])=156.279 ($p<0.001$) for operative intervention, χ^2 (8 d.f.)= 6.492 ($p=0.592$) for mortality, χ^2 (8 d.f.)= 247.873 ($p<0.001$) for ICU admission, and χ^2 (8 d.f.)= 247.873 ($p<0.001$) for mechanical ventilation use. Area under the ROC curve for logistic model discrimination were 0.830 for operative intervention, 0.965 for mortality, 0.786 for ICU admission, and 0.869 for mechanical ventilation use. In linear regression models for continuous outcomes, R^2=0.246 and R^2=0.381 for hospital LOS and ICU LOS, respectively.

Multivariate examination of pairwise interaction effects indicated a significant effect of benzodiazepine and opiate together on operative intervention (OR_{BENZ} 3.089 $p<0.001$; OR_{OPIA} 2.679, $p<0.001$; $OR_{BENZ*OPIA}$ 0.570, $p=0.001$), mortality (OR_{BENZ} 0.498 $p=0.004$; OR_{OPIA} 0.484, $p=0.011$; $OR_{BENZ*OPIA}$ 5.068, $p=0.001$), Log_{10}(Hospital LOS) (RC_{BENZ} 0.219 $p<0.001$; RC_{OPIA} 0.106, $p<0.001$; $RC_{BENZ*OPIA}$ −0.103, $p<0.001$), and Log_{10}(ICU LOS) (RC_{BENZ} 0.203 $p<0.001$; RC_{OPIA} 0.170, $p<0.001$; $RC_{BENZ*OPIA}$ −0.126, $p=0.007$). In other words, concurrent benzodiazepine and opiate use was associated with higher mortality, and likely therefore lower rates of operative intervention, shorter hospital LOS, and shorter ICU LOS. In addition, there was a significant effect of amphetamine and barbiturate together on mortality (OR_{AMPH} 0.467 $p=0.006$; OR_{BARB} 0.927, $p=0.920$; $OR_{AMPH*BARB}$ 22.768, $p=0.022$) and Log_{10}(Hospital LOS) (RC_{AMPH} 0.043 $p<0.001$; RC_{BARB} 0.198, $p<0.001$; $RC_{AMPH*BARB}$ −0.181, $p=0.040$). Similar to the combination of benzodiazepine and opiate use, concurrent amphetamine and barbiturate use were associated with higher mortality and shorter hospital LOS.

Discussion

Prior to the present study, published literature examining the impact of pre-injury controlled substance use on clinical outcomes following trauma have each focused on a limited number

of drugs. Specifically, studies investigating pre-injury amphetamine use have reported inconsistent results. Pre-injury amphetamine use has been significantly associated with increased LOS (13), increased mortality (11), and increased ICU admission (10). However, both the significance and directional trend of these differences varied across studies (10-14). Although the present study also found that amphetamine-positivity was significantly associated with longer LOS, it was also associated with lower mortality and decreased ICU admission. A ten year difference in study time frame represents a possible explanation for this discrepancy. During the late 2000's amphetamine prescriptions for Attention Deficit Hyperactivity Disorder increased dramatically. Thus, the present study examines a fundamentally different patient population than those of previous studies (5).

The results of the present study also correspond well with previous studies of pre-injury benzodiazepine, cocaine, and opiate use. Consistent with the results of the current study, a recent study found increased LOS, increased ICU LOS, and increased mechanical ventilation in benzodiazepine-positive patients (15). Before this study, pre-injury cocaine use has not been established as a significant predictor of outcomes following trauma (16-19, 21). However, a combination of cocaine and ethanol yields the toxic metabolic cocaethylene, which has been significantly associated with increased ICU admission (20). In the present study, cocaine use was associated with longer ICU LOS after adjusting for differences in patient characteristics, but this effect was not significantly impacted by concurrent alcohol use. Another recent study found a significant association between pre-injury opiate use and increased LOS following trauma, but only in less severely injured patients with ISS<15 (22). After controlling for ISS among other patient characteristics, the present study also identified a significant association between opiate use and increased LOS.

The current study identified a greater number of significant associations between each controlled substance and clinical outcomes following trauma compared to previously published investigations. This dissimilarity may be attributed to a difference in statistical power across studies. In comparison to other single center investigations, the present study assessed a substantially larger patient population with a greater number of patients testing positive for each drug.

This is the first clinical outcomes study to include all controlled substances tested in a standard admission urine toxicology screen. Its results indicate a high prevalence of pre-injury controlled substance use in trauma patients. Additionally, trauma patients frequently use multiple drugs prior to presentation. In fact, patients testing positive for at least two controlled substances outnumber patients who test positive for any one specific controlled substance. Since the previously published literature tends to focus on an individual drug class and often excludes patients testing for multiple drugs, they fail to represent a substantial segment of drug-positive trauma patients. By including poly-drug-positive patients, the present study is able to create a more comprehensive model characterizing trauma patients who use controlled substances. Furthermore, the present study identified significant pairwise interactions between benzodiazepine and opiate use, as well as amphetamine and barbiturate use. Both of these pairwise interactions were associated with substantially higher rates of mortality than any of their constituent controlled substances alone. In fact, benzodiazepine and opiate use were protective against mortality when used

alone, but their combination was associated with one of the highest OR identified in the study ($OR_{BENZ*OPIA}$ 5.068, p=0.001).

The current study is also the first study to compare the relative impact of each controlled substance on clinical outcomes following trauma. After adjusting for differences in patient characteristics, a comparison of main effects odds ratios and regression coefficients indicates that PCP has the greatest impact on mortality compared to other controlled substances. Similarly, benzodiazepine use contributes the greatest effect on operative intervention, ICU admission, mechanical ventilation, hospital LOS, and ICU LOS in comparison to other drugs.

Several limitations concern the present study. First, although all drugs included in the hospital's standard urine toxicology screen were included for analysis, the standard screen does not comprehensively capture all drugs. For example, cannabinoids are not included in the standard panel and must be ordered separately; therefore the present study did not include these drugs in its analysis. Nonetheless, the present study builds upon previous studies, which have examined a limited subset of controlled substances typically included in a standard urine toxicology screen. Second, use of controlled substances was analyzed as binary variables instead of continuous drug levels. Although this methodology practically incorporates the information available to most clinicians, it precludes analysis of a dose-dependent relationship between controlled substances and outcomes. Third, urine toxicology and blood alcohol panels are routinely ordered only for patients with altered mental status; for all other patients, these admission screens are ordered at the discretion of the evaluating trauma team. Due to the retrospective design of the current study, some data are absent, and not all patients who used controlled substances prior to presentation were captured in this study. This may introduce some selection bias and represents a weakness of this study.

Another potential study weakness concerns the regression models' somewhat low predictive power. In the case of linear regression models for hospital LOS and ICU LOS, low R^2 values (0.246 and 0.381, respectively) suggest the models account for only a modest fraction of the variation in the two clinical outcomes. Indeed, patients suffering from trauma are complex, and their hospital LOS and ICU LOS are likely influenced by many factors unaccounted for in this study's regression models. In the context of the present study, analyzing regression coefficients is useful for evaluating directional trends and comparing the relative impact of each controlled substance. Computing quantitative predictions of clinical outcomes would not be clinically practical. Instead, the results of multivariable analysis should be interpreted in a broader sense: benzodiazepine, barbiturate, opiate, cocaine, and amphetamine use are associated with longer LOS, while barbiturate, benzodiazepine, and opiate use are associated with longer ICU LOS.

Similarly, calibration of logistic regression models for operative intervention ($p<0.001$), ICU admission ($p<0.001$), and ventilator use ($p<0.001$) suggest a significant difference between predicted and observed mortality rates across the entire study population; only calibration of the logistic regression model for mortality (p=0.592) indicated robust goodness of fit. Studies with large sample sizes frequently fail the Hosmer and Lemeshow Test, and "a significant Hosmer-Lemeshow test does not necessarily mean that a predictive model is not

useful or suspect" (25). In fact, discrimination of logistic regression models for all clinical outcomes were excellent. Area under the ROC curves for operative intervention, mortality, ICU admission, and mechanical ventilation use were 0.830, 0.965, 0.786, and 0.869, respectively. This indicates high sensitivity and specificity for all logistic regression models.

Knowledge of the relationship between specific drugs and outcomes like operative intervention or mechanical ventilation can help clinicians identify which patients are likely to require these treatments before they are emergently needed. Patients sustaining traumatic injury are often characterized by fluctuating stability and evolving clinical needs. For example, a benzodiazepine-positive patient may not necessarily require mechanical ventilation immediately after traumatic injury. However, as patients who test positive for benzodiazepine are more likely to require ventilator support compared to patients who test negative, the results of the present study may enhance the efficiency and speed at which ventilation need is identified in these patients.

Furthermore, recognizing the prognostic value of drug positivity can help risk stratify patients and help clinicians optimize patient care. Patients testing positive for amphetamine are 0.5 times less likely to die than patients testing negative while patients testing positive for barbiturate are 1.9 times more likely to die than those testing negative. Knowledge of patients' use of these drugs can help clinicians efficiently allocate their focus. Maintaining an equal level of vigilance for each individual patient regardless of their health status—drug positivity included—is neither ideal nor practical.

In conclusion, as use of controlled substances continues to increase, healthcare providers must care for a growing population of patients under their influence. Trauma patients frequently present with positive toxicology screens for at least one drug. There exists a need to better characterize these patients and identify those at highest risk of adverse clinical outcomes. The results presented herein suggest that pre-injury use of amphetamine, barbiturate, benzodiazepine, cocaine, opiate, and PCP have significant and variable impact on clinical outcomes following trauma. Recognition of these patterns may help clinicians risk-stratify trauma patients and efficiently anticipate and allocate their limited resources.

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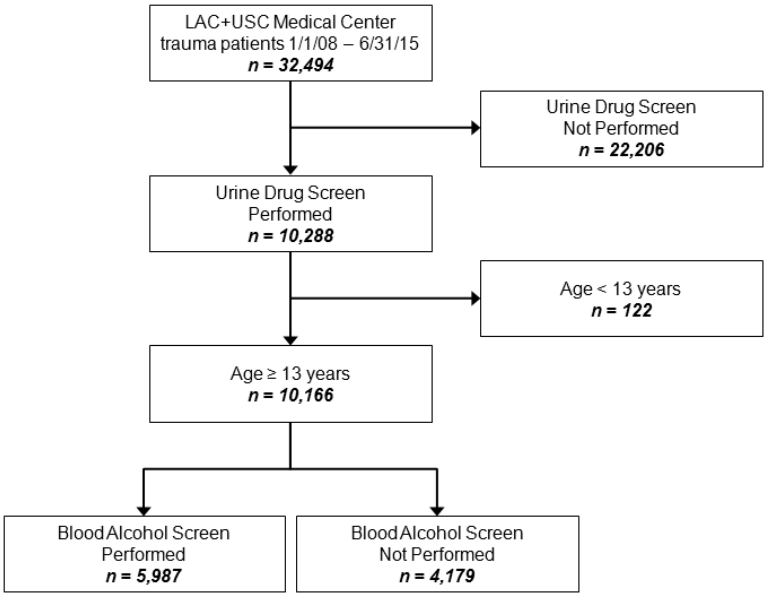

Figure 1.
Study inclusion criteria.

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Table 1

Patient Characteristics

	All Patients (n=10,166)	Completely Negative (n=5,621)	Amphetamine Only (n=754)	Barbiturate Only (n=63)	Benzo Only (n=501)	Cocaine Only (n=553)	Opiate Only (n=1,368)	PCP Only (n=53)	Multiple Drugs (n=1,253)	p-value
Age (years) *	39.2 ± 16.8	40.3 ± 17.7	32.9 ± 12.4	52.4 ± 17.8	38.8 ± 17.1	41.7 ± 13.2	37.5 ± 16.9	44.4 ± 14.9	37.7 ± 14.1	<0.001
Sex- Male †	8,076 (79.4%)	4,386 (78%)	595 (78.9%)	51 (81%)	435 (86.8%)	453 (81.9%)	1,070 (78.2%)	40 (75.5%)	1,046 (83.5%)	<0.001
Admission SBP *	133.9 ± 23.8	134.8 ± 23.7	131.4 ± 23.5	135.4 ± 22.9	131 ± 27.4	134.6 ± 24.6	135 ± 21.9	139.7 ± 30.5	130.6 ± 24.0	<0.001
Admission GCS **	15.0 (14.0-15.0)	15.0 (14.0-15.0)	15.0 (14.0-15.0)	14.0 (13.0-15.0)	14.0 (9.0-15.0)	15.0 (14.0-15.0)	15.0 (15.0-15.0)	15.0 (13.5-15.0)	15.0 (14.0-15.0)	<0.001
ISS **	5.0 (2.0-13.0)	5.0 (1.0-10.0)	5.0 (1.0-11.0)	2.0 (1.0-9.0)	10.0 (5.0-22.0)	5.0 (1.0-10.0)	9.0 (5.0-14.0)	4.0 (1.0-9.0)	9.0 (4.0-14.0)	<0.001
AIS *										
Head and Neck	3.7 ± 2.0	3.9 ± 2.0	3.6 ± 2.1	2.2 ± 1.2	3.7 ± 1.8	2.9 ± 1.8	3.0 ± 1.6	3.7 ± 2.1	3.3 ± 1.8	<0.001
Face	2.3 ± 1.5	2.3 ± 1.5	2.7 ± 1.6	1.4 ± 0.5	2.3 ± 1.4	1.9 ± 1.2	2.2 ± 1.4	2.5 ± 2.4	2.6 ± 1.5	0.003
Chest	2.8 ± 1.1	2.7 ± 1.2	2.9 ± 1.1	3.3 ± 1.5	2.7 ± 1.0	2.8 ± 1.1	2.7 ± 1	2.0 ± 1.2	3.1 ± 1.0	0.004
Abdomen & Pelvis	2.4 ± 1.0	2.3 ± 1.1	2.5 ± 1.1	1.7 ± 0.3	2.6 ± 1.1	2.3 ± 1.0	2.4 ± 0.8	1.5 ± 0.7	2.6 ± 0.9	0.016
Extremities	2.3 ± 0.7	2.1 ± 0.7	2.2 ± 0.7	2.0 ± 1.0	2.4 ± 0.7	2.1 ± 0.8	2.4 ± 0.6	1.8 ± 0.5	2.4 ± 0.8	<0.001
External	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.0	1.0 ± 0.1	1.0 ± 0.2	1.0 ± 0.1	1.0 ± 0.0	1.0 ± 0.3	0.182
Trauma Type †										
Blunt	8,465 (83.3%)	4,965 (88.3%)	543 (72%)	63 (100%)	399 (79.6%)	434 (78.5%)	1,152 (84.2%)	46 (86.8%)	863 (68.9%)	<0.001
Penetrating	1,735 (17.1%)	665 (11.8%)	217 (28.8%)	0 (0.0%)	106 (21.2%)	122 (22.1%)	221 (16.2%)	7 (13.2%)	397 (31.7%)	<0.001
Other	18 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	6 (0.4%)	0 (0.0%)	11 (0.9%)	<0.001

*Continuous variables expressed as mean values ± standard deviation; P value calculated with one-way ANOVA

†Categorical variables expressed as patients (%); P value calculated with Chi-square test.

**Continuous variables expressed as median (interquartile range); P value calculated with one-way ANOVA

SBP, systolic blood pressure; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; AIS, Abbreviated Injury Scale

Table 2

Injury Mechanisms

	All Patients (n=10,166)	Completely Negative (n=5,621)	Amphetamine Only (n=754)	Barbiturate Only (n=63)	Benzo Only (n=501)	Cocaine Only (n=553)	Opiate Only (n=1,368)	PCP Only (n=53)	Multiple Drugs (n=1,253)	p-value
Motor vehicle collision										
Motorcycle/moped	203 (2.0%)	76 (1.4%)	13 (1.7%)	0 (0.0%)	17 (3.4%)	5 (0.9%)	66 (4.8%)	0 (0.0%)	26 (2.1%)	<0.001
Unenclosed vehicle	125 (1.2%)	73 (1.3%)	10 (1.3%)	0 (0.0%)	4 (0.8%)	3 (0.5%)	25 (1.8%)	0 (0.0%)	10 (0.8%)	0.158
Enclosed vehicle	1,597 (15.7%)	993 (17.7%)	114 (15.1%)	0 (0.0%)	52 (10.4%)	50 (9%)	240 (17.5%)	6 (11.3%)	142 (11.3%)	<0.001
Passenger Space Intrusion										
<12in occupied space	652 (6.4%)	374 (6.7%)	49 (6.5%)	2 (3.2%)	24 (4.8%)	24 (4.3%)	120 (8.8%)	5 (9.4%)	54 (4.3%)	<0.001
12-18in occupied space	2 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.324
>18in occupied space	2 (0.0%)	1 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.582
Pedestrian/bike thrown/run over										
≤20 MPH	1,088 (10.7%)	582 (10.4%)	55 (7.3%)	7 (11.1%)	50 (10%)	68 (12.3%)	195 (14.3%)	7 (13.2%)	124 (9.9%)	<0.001
>20 MPH	432 (4.2%)	260 (4.6%)	26 (3.4%)	1 (1.6%)	16 (3.2%)	13 (2.4%)	70 (5.1%)	1 (1.9%)	45 (3.6%)	0.035
Fall										
≤15 feet	2,334 (23%)	1,529 (27.2%)	108 (14.3%)	42 (66.7%)	130 (25.9%)	104 (18.8%)	199 (14.5%)	13 (24.5%)	209 (16.7%)	<0.001
>15 feet	173 (1.7%)	69 (1.2%)	19 (2.5%)	0 (0.0%)	10 (2.0%)	13 (2.4%)	28 (2.0%)	0 (0.0%)	34 (2.7%)	0.002
Assault	861 (8.5%)	462 (8.2%)	85 (11.3%)	0 (0.0%)	39 (7.8%)	111 (20.1%)	55 (4.0%)	3 (5.7%)	106 (8.5%)	<0.001
Gunshot	452 (4.4%)	146 (2.6%)	71 (9.4%)	0 (0.0%)	30 (6.0%)	22 (4.0%)	58 (4.2%)	2 (3.8%)	123 (9.8%)	<0.001
Stabbing	824 (8.1%)	336 (6%)	102 (13.5%)	0 (0.0%)	45 (9.0%)	80 (14.5%)	99 (7.2%)	4 (7.5%)	158 (12.6%)	<0.001
Thermal burn	7 (0.1%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.1%)	0 (0.0%)	4 (0.3%)	0.016
Electrical shock	2 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0.889
Other	385 (3.8%)	200 (3.6%)	30 (4.0%)	4 (6.3%)	25 (5.0%)	14 (2.5%)	50 (3.7%)	1 (1.9%)	61 (4.9%)	0.138
Unknown	506 (5.0%)	352 (6.3%)	35 (4.6%)	5 (7.9%)	30 (6.0%)	27 (4.9%)	8 (0.6%)	9 (17.0%)	40 (3.2%)	<0.001

Categorical variables expressed as patients (%); P value calculated with Chi-square test.

Table 3

Univariable Analyses of Clinical Outcomes Stratified by Pre-injury Controlled Substance Group

	Completely Negative (n=5,621) A	Amphetamine Only (n=754) B	Barbiturate Only (n=63) C	Benzodiazepine Only (n=501) D	Cocaine Only (n=553) E	Opiate Only (n=1,368) F	PCP Only (n=53) G	Multiple Drugs (n=1,253) H
Operative Intervention *	813 (16.9%) BDFH	173 (29.8%) ADFHG	5 (8.6%) DFH	224 (80.9%) ABCEFG	104 (23.2%) DFH	489 (55.6%) ABCDEGH	1 (1.9%) BDFH	537 (75.0%) ABCEFG
Craniotomy/ Craniectomy	129 (2.3%) DF	19 (2.6%) DF	2 (3.3%)	30 (6.4%) ABFH	14 (2.6%) F	7 (0.5%) ABDE	0 (0.0%)	19 (1.5%) D
Thoracotomy/ Sternotomy	37 (0.7%) H	3 (0.4%)	0 (0.0%)	8 (1.6%)	6 (1.1%)	5 (0.4%) H	0 (0.0%)	21 (1.7%) AF
Laparotomy	171 (3.1%) BDH	42 (5.9%) ADH	0 (0.0%)	94 (23.1%) ABEF	26 (4.9%) DH	45 (3.4%) DH	0 (0.0%)	172 (15.9%) ABEF
Mortality *	259 (4.8%) BF	14 (1.9%) AD	1 (1.6%)	31 (6.6%) BF	18 (3.4%)	21 (1.6%) AD	2 (3.9%)	41 (3.4%)
ICU Admission *	937 (20.0%) D	107 (16.5%) DH	13 (26.0%)	196 (64.3%) ABEFGH	81 (17.2%) D	195 (16.6%) DH	9 (20.5%) D	248 (24.7%) BDF
Mechanical Ventilation *	426 (8.2%) DF	47 (6.6%) DF	3 (5.0%) D	148 (41.9%) ABCEFH	36 (7.0%) DF	35 (2.6%) ABDEH	5 (10.4%)	117 (10.3%) DF
Hospital Length of Stay †	6.2 ± 11.8 DFH	7.3 ± 19.0 DH	8.5 ± 7.9	13.7 ± 17.3 ABEFGH	8.1 ± 22.7 DH	8.0 ± 12.9 ADH	5.1 ± 6.5 D	10.8 ± 17.8 ABDEF
ICU Length of Stay †	3.5 ± 7.1 DEFH	4.1 ± 6.6 DH	5.0 ± 4.2	7.7 ± 10.0 AB	6.3 ± 13.6 A	5.4 ± 8.8 A	2.5 ± 3.1	7.0 ± 12.2 AB

Superscripts A-H represent significant differences between listed proportions and corresponding drug categories

* Categorical variables expressed as patients (%); Significance determined with Chi-square test with post hoc comparisons of proportions with Bonferroni correction ($\alpha = 0.05$).

† Continuous variables expressed as mean values ± standard deviation; Significance determined with one-way ANOVA with post hoc Bonferroni correction ($\alpha = 0.05$).

Table 4

Multivariable Regression of Outcomes with Pre-injury Controlled Substance Main Effects as Predictors

Clinical Outcome	Drug	Odds Ratio	Regression Coefficient	95% Confidence Interval	P-value
Operative Intervention	Amphetamine	1.327	—	1.144 to 1.541	<0.001
	Barbiturate	0.518	—	0.275 to 0.977	0.042
	Benzodiazepine	2.541	—	2.173 to 2.972	<0.001
	Cocaine	1.127	—	0.947 to 1.341	0.179
	Opiate	2.446	—	2.170 to 2.757	<0.001
	PCP	0.412	—	0.224 to 0.759	0.004
Mortality	Amphetamine	0.498	—	0.290 to 0.856	0.012
	Barbiturate	1.419	—	0.410 to 4.909	0.580
	Benzodiazepine	0.715	—	0.477 to 1.073	0.105
	Cocaine	0.818	—	0.477 to 1.403	0.466
	Opiate	0.792	—	0.505 to 1.243	0.311
	PCP	3.488	—	1.167 to 10.43	0.025
ICU Admission	Amphetamine	0.732	—	0.614 to 0.873	0.001
	Barbiturate	1.622	—	1.039 to 2.532	0.033
	Benzodiazepine	1.919	—	1.640 to 2.245	<0.001
	Cocaine	0.786	—	0.646 to 0.958	0.017
	Opiate	0.808	—	0.701 to 0.932	0.003
	PCP	0.845	—	0.493 to 1.448	0.539
Mechanical Ventilation	Amphetamine	0.738	—	0.569 to 0.956	0.021
	Barbiturate	0.950	—	0.455 to 1.984	0.891
	Benzodiazepine	3.327	—	2.729 to 4.056	<0.001
	Cocaine	0.789	—	0.587 to 1.060	0.116
	Opiate	0.497	—	0.389 to 0.636	<0.001
	PCP	1.189	—	0.575 to 2.460	0.640
Log_{10}(Hospital Length of Stay)	Amphetamine	—	0.031	0.010 to 0.052	0.004
	Barbiturate	—	0.142	0.077 to 0.207	<0.001
	Benzodiazepine	—	0.181	0.157 to 0.205	<0.001
	Cocaine	—	0.037	0.013 to 0.061	0.003
	Opiate	—	0.090	0.072 to 0.108	<0.001
	PCP	—	0.002	−0.062 to 0.066	0.940
Log_{10}(ICU Length of Stay)	Amphetamine	—	0.002	−0.042 to 0.046	0.929
	Barbiturate	—	0.140	0.021 to 0.259	0.021
	Benzodiazepine	—	0.170	0.131 to 0.209	<0.001
	Cocaine	—	0.051	−0.002 to 0.104	0.057
	Opiate	—	0.139	0.100 to 0.178	<0.001
	PCP	—	0.077	−0.058 to 0.213	0.263

Multivariable analysis adjusted for age, sex, admission systolic blood pressure, admission Glasgow Coma Score, Injury Severity Score, and mechanism of injury.