



Original Contribution

## Stimulant drugs are associated with violent and penetrating trauma<sup>☆,☆☆,★</sup>

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### ABSTRACT

**Background:** Substance abuse is associated with traumatic injuries. Prior studies of drug use and injury have relied on urine drug of abuse screens, which have false positives, false negatives and inability to detect novel drugs. Our study characterizes the relationship between injury mechanism and drugs of abuse detected in serum via confirmatory testing.

**Methods:** This prospective observational study was conducted from Jan–Sept 2012 at a level 1 trauma center on trauma patients > 13 years who had blood drawn for routine tests. Demographic, injury and standard laboratory data were abstracted from patient charts. Comprehensive serum drug testing was done using liquid chromatography-time-of-flight mass spectrometry (LC-TOF/MS, LC1200-TOF/MS 6230, Agilent, Santa Clara, CA). **Results:** Of 272 patients, 71.0% were male, 30.5% had violent injury type and 32.4% had a penetrating injury mechanism. Violent injury type and penetrating injury mechanisms were more frequent in patients who were male, younger age, Black, or Hispanic ( $p < 0.05$  for all). LC-TOF/MS showed that 46.0% were positive for at least one drug. Stimulant drugs were associated with violent injury type (OR 2.9; 95% CI 1.64–5.15) and penetrating injury mechanism (OR 3.3; 95% CI 1.86–5.82). Tobacco use was associated with violent injury type (OR 3.9; 95% CI 2.25–6.77) and penetrating injury mechanism (OR 4.14; 95% CI 2.4–7.14).

**Conclusions:** Many drugs are present in trauma patients that are not routinely detected on urine drug of abuse tests. Both stimulant drugs and cigarette smoking are indicators of multidimensional hazardous behaviors, which were associated with more violent and penetrating trauma.

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## 1. Background

The American College of Surgeons (ACS) supports routine drug testing on trauma patients, as evidenced by its inclusion in the National Trauma Data Bank [1], a practice which has been both supported and refuted in the medical literature [2–5]. Patients meeting trauma activation guidelines test positive for illicit drugs more often than those who do

not meet activation criteria [2]. There are several limitations to urine drug of abuse (UDOAs) screening tests routinely performed in hospitals, including limited drug coverage, false positives, and false negatives due to low sensitivity and specificity of the assays [5]. UDOAs are not necessarily an indicator of acute intoxication, but rather only of use, since most drugs will be excreted in the urine long after blood levels have declined below those associated with intoxication. Moreover, studies have shown that UDOA results do not alter patient care [4,5].

In addition, a number of drugs are not detected by standard urine drug of abuse testing, including many stimulant drugs. Stimulants encompass a wide variety of compounds, including cocaine, methamphetamine, methylenedioxymethamphetamine (MDMA), phencyclidine (PCP), synthetic cathinones (bath salts), and other related compounds. Cocaine has been associated with interpersonal violence and penetrating trauma [6–9]. Methamphetamine has been associated with violence, blunt trauma, and burn injuries without clear correlation between drug

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use and mechanism of trauma [10,11]. PCP has been associated with violent behavior [12]. Tobacco use is common among abusers of illicit drugs and is also associated with risk-taking behavior. No study to date has analyzed the associations between a broad panel of stimulant drugs and injury mechanism or laboratory confirmed tobacco use and mechanism of traumatic injury.

The primary objectives of this study were to 1) determine which drugs are present in trauma patients that are not detectable by standard urine drug of abuse screening tests, 2) determine if stimulant drugs are associated with more violent than nonviolent injury type, and 3) determine if stimulant drugs are associated with more penetrating than blunt mechanisms of traumatic injury. The secondary objectives were to 1) determine if non-stimulant drugs are associated with more blunt than penetrating mechanisms of traumatic injury and 2) determine if tobacco use was associated with more violent or penetrating mechanisms than nonviolent or blunt mechanisms of traumatic injury.

## 2. Methods

This prospective observational study was conducted at San Francisco General Hospital, an ACS-verified Level 1 trauma center in San Francisco, CA. The catchment area includes urban and suburban populations covering over 1.5 million people. There are approximately 65,000 emergency department (ED) visits and 4000 trauma patients treated annually. Approval was obtained from the University of California San Francisco Committee for Human Research.

From January to September 2012, a convenience sample of non-consecutive patients was prospectively enrolled. A convenience sample was used due to variable availability of volunteer study staff during the study period. Patients presenting during days, nights, and weekends were included in the study. Any patient with major trauma age 13 and above who had blood drawn for routine laboratory tests was eligible for enrollment. For the purposes of this study, major trauma was defined as any patient treated for a traumatic injury in one of the 3 trauma resuscitation bays upon ED arrival. In this ED, almost all major trauma patients were treated in the trauma resuscitation bays, and a paper book log was kept by the ED clerks of every patient roomed in that area. Since this study was performed prior to the transition to an electronic medical record, this paper-based log was deemed the most reliable source for locating major trauma patients, especially since the goal was to enroll all-comers, not just those physically present in the ED during study volunteer hours.

Data were retrospectively abstracted from medical records and included: demographics (age, sex, race, city of residence), self-reported social habits, home medications, medications given in first 24 h of hospitalization, chief complaint, mechanism of injury, urine drug of abuse (UDOAs) screen results, blood alcohol concentration (BAC), discharge diagnoses, and final disposition. UDOA screening at this institution detects amphetamines, barbiturates, benzodiazepines, cocaine metabolite (benzoylecgonine), and opiates (heroin, methadone, oxycodone, oxymorphone, codeine, morphine, hydrocodone, hydromorphone). UDOA and BAC were ordered at the discretion of the treating physicians and were not additionally performed for the purposes of this study. Serum samples had additional comprehensive drug testing performed only for the purposes of this study, as described below. It is not a test routinely performed on ED or trauma patients. Statistical analysis was performed to evaluate the association between stimulant drugs and injury type and mechanism, and tobacco smoking and injury type and mechanism, reported as odds ratios with 95% confidence intervals and p values (SPSS version 23.0, IBM Corp, Armonk, NY). Violent injury type was defined in this study as interpersonal violence: those with gunshot wounds and stab wounds inflicted by others, and blunt object assault. Accidental or self-inflicted gunshot and stab wounds were considered non-violent injury type.

Leftover blood samples from the initial blood draw at time of ED presentation were frozen at  $-80^{\circ}\text{C}$  until batches were ready for analysis.

All study subjects had enough leftover serum available for testing. Comprehensive drug testing was performed on serum samples using liquid chromatography-time-of-flight mass spectrometry (LC-TOF/MS, LC1200-TOF/MS 6230, Agilent Technologies, Santa Clara, CA). Each sample's total ion chromatogram (TIC) was analyzed using Agilent MassHunter Qualitative Analysis software, to determine the presence of potential drug and drug metabolites. TICs were cross-referenced with a drug of abuse panel containing 214 drugs (41 phenylalkylamines [amphetamines and phenethylamines], 32 benzodiazepines, 28 opioids, 24 antidepressants, 16 barbiturates, 14 antihistamines, 13 analgesics, 10 sedative/hypnotics, 10 psychotropic alkaloids, 10 anesthetics, 9 stimulants, and 7 muscle relaxants) as well as nicotine and cotinine (nicotine metabolite). Serum cotinine is considered a surrogate marker for tobacco use [13]. Details of the LC/TOF-MS analysis have been published previously [14]. Once initial drugs were identified in serum samples, home medications and initial in-hospital medications were removed to create the final list of drugs present in each subject. This was done in order to have as clear a picture as possible of illicit drugs and unprescribed medications present in each case. In order to obtain an unbiased baseline rate of urine drug and blood alcohol testing on trauma patients at our institution, providers were blinded to this study's testing protocols.

## 3. Results

During the study period, 272 subjects were enrolled, of which 71.0% were male. Violent injury type and penetrating injury mechanisms were present more often in patients who were males, younger age, Black, or Hispanic (Table 1). Routine UDOA screens were performed on 14.3% patients in the study cohort; 10/88 (11.4%) penetrating and 29/184 (15.8%) blunt mechanisms of trauma. Of the UDOA's performed, 30/39 (76.9%) were positive for at least one drug class; 9/10 (90.0%) penetrating and 21/29 (72.9%) blunt. BACs were obtained on 56/272 patients (20.6%); 10/88 (11.4%) penetrating and 46/184 (25.0%) blunt. Of the BACs measured, 40/56 (71.4%) were above the legal limit ( $>0.08\%$ ); 6/10 (60.0%) penetrating and 34/46 (73.9%) blunt mechanisms of trauma.

Comprehensive serum drug testing revealed that 125/272 (46.0%) of the study cohort were positive for at least one drug. Stimulant drugs were categorized into amphetamines (phenethylamines, amphetamines, cathinones) and non-amphetamines (cocaine, PCP, piperazines) for the purposes of this study. There were no significant differences in age, sex or race for the presence of stimulant drugs as detected by LC/TOF-MS. Eighteen different stimulant drugs were detected, of which 3 were non-amphetamines and 15 were amphetamines and amphetamine derivatives (Table 2). Only 5/18 (27.8%) stimulants would be detected on a standard hospital UDOA, which screens for cocaine, amphetamines and PCP. 34 patients tested positive for the remaining 13 stimulant drugs that would normally go undetected. Cocaine was detected in 23 (26.1%) and MDA in 13 (14.8%) penetrating trauma patients. In blunt trauma patients, cocaine was detected in 15 (8.2%), MDMA in 7 (3.8%), and MDA in 6 (3.3%). Detected non-stimulant drugs are listed in Table 3. The drugs listed in the antidepressants, antihistamines, and Other categories would not be detected on a routine UDOA screen. Zolpidem, an atypical benzodiazepine undetectable on standard UDOAs, was found in 4 penetrating (4.6%) and 6 blunt (3.3%) trauma patients. 3/10 (30.0%) opiates/opioids would be detected on a routine UDOA screen, while the others in this class require specific testing to detect.

All types of stimulants were detected in penetrating trauma (39.8%) patients more frequently than blunt trauma (17.4%) (Table 4). When broken down by specific mechanism of injury, a larger proportion was due to stimulant positive stab wound cases (49.2%) than gunshot wounds (20.7%). Stimulant drugs were associated with violent injury type (OR 2.9; 95% CI 1.64–5.15) and penetrating injury mechanism (OR 3.3; 95% CI 1.86–5.82) (Table 5). The association persisted when

**Table 1**  
Patient demographics.

	n	Gender, n (%)		Race, n (%)					Mean age (SD)
		Male	Female	White	Black	Hispanic	Asian/Pacific Islander	Other/unknown	
<b>Injury type</b>									
Non-violent	189	117 (61.9)	72 (38.1)	89 (47.1)	15 (7.9)	30 (15.9)	41 (21.7)	–	50.9 (22.2)
Violent	83	76 (91.6)	7 (8.4)	11 (13.3)	39 (47.0)	26 (31.3)	5 (6.0)	2 (2.4)	31.4 (12.2)
p value		<0.001		<0.001	<0.001	0.004	0.002	0.16	<0.001
<b>Injury mechanism</b>									
Blunt	184	115 (62.5)	69 (37.5)	86 (46.7)	15 (8.2)	28 (15.2)	41 (22.3)	14 (7.6)	51.3 (22.3)
Motor vehicle collision	48	27 (56.3)	21 (43.8)	19 (39.6)	4 (8.3)	9 (18.9)	13 (27.1)	2 (4.2)	40.2 (16.8)
Motorcycle collision	27	22 (81.5)	5 (18.5)	22 (81.5)	1 (3.7)	1 (3.7)	2 (7.4)	1 (3.7)	38.2 (12.1)
All vehicular injury <sup>a</sup>	76	49 (64.5)	27 (35.5)	42 (55.3)	5 (6.6)	10 (13.2)	15 (19.7)	3 (4.0)	39.4 (15.1)
Ground level fall	57	30 (52.6)	27 (47.4)	21 (36.8)	6 (10.5)	9 (15.8)	15 (26.3)	6 (10.5)	68.5 (20.1)
Fall from height	50	36 (72.0)	14 (28.0)	23 (46.0)	4 (8.0)	8 (16.0)	12 (24.0)	3 (6.0)	50.2 (21.7)
Penetrating	88	78 (88.6)	10 (11.4)	14 (15.9)	39 (44.3)	28 (31.8)	5 (5.7)	2 (2.3)	31.7 (12.3)
Gunshot wound	29	26 (89.7)	3 (10.3)	2 (6.9)	18 (62.1)	5 (17.2)	2 (6.9)	2 (6.9)	25.8 (10.2)
Stab wound	59	52 (88.1)	7 (11.9)	12 (20.3)	21 (35.6)	23 (39.0)	3 (5.1)	–	34.5 (12.3)
p value <sup>b</sup>		<0.001		<0.001	<0.001	0.002	0.001	0.1	<0.001
<b>Serum drug results</b>									
Stimulant	68	50 (73.5)	18 (26.5)	27 (39.7)	18 (26.5)	14 (20.6)	8 (11.8)	1 (1.5)	45.6 (22.7)
Amphetamine derivative	37	26 (70.3)	11 (29.7)	17 (45.9)	6 (16.2)	7 (18.9)	6 (16.2)	1 (2.7)	45.1 (20.9)
Non-amphetamine	41	33 (80.5)	8 (19.5)	15 (36.6)	14 (34.1)	10 (24.4)	2 (4.9)	–	38.3 (15.4)
No stimulant	204	143 (70.1)	61 (29.9)	73 (35.8)	36 (17.6)	42 (20.6)	38 (18.6)	15 (7.4)	45.4 (18.9)
p value <sup>c</sup>		0.59		0.56	0.11	1	0.19	0.081	0.57

<sup>a</sup> Includes all motor vehicle and motorcycle collisions and one pedestrian versus auto case.  
<sup>b</sup> Comparison of all blunt versus all penetrating injury mechanisms.  
<sup>c</sup> Comparison includes all stimulant versus all no stimulant results.

the stimulant positive groups were stratified into amphetamine positive and non-amphetamine stimulant positive groups.

Although both the opiates/opioids and benzodiazepines are central nervous system depressants, they had different patterns of prevalence in the study cohort (Table 4). Opiates/opioids were present in more blunt trauma patients (14.1%) than penetrating (8.0%); typical and atypical benzodiazepines were present in 13.6% of penetrating and 4.9% of blunt trauma patients. Motorcycle collisions and fall from height accounted for a large proportion of stimulant and opioid positive blunt trauma cases. 20% of fall from height patients had antidepressants in their system. Evidence of tobacco use was associated with violent injury type (OR 3.9; 95% CI 2.25–6.77) and penetrating injury mechanism (OR 4.14; 95%CI 2.4–7.14) (Table 6).

**Table 2**  
Detected stimulant drugs.

Drug	Number of cases
Cocaine <sup>a,b</sup>	38
Methylenedioxyamphetamine (MDA) <sup>c</sup>	19
Methylenedioxyamphetamine (MDMA)	9
Methamphetamine <sup>a</sup>	5
1,3-Benzodioxolylbutanamine (BDB)	3
3,4-Dimethoxyamphetamine (3,4-DMA)	3
Methylphenidate <sup>a</sup>	3
Phenylpropanolamine (PPA)	3
2C-T-2	2
Benzylpiperazine (BZP)	2
Mephedrone	2
Pseudoephedrine	2
2C-T-7	1
Amphetamine <sup>a</sup>	1
2,5-Dimethoxy-4-ethylamphetamine (DOEt)	1
Paramethoxyamphetamine (PMA)	1
Paramethoxymethamphetamine (PMMA)	1
Phencyclidine (PCP) <sup>a</sup>	1

<sup>a</sup> Routinely detected on standard hospital urine drug of abuse screening tests.  
<sup>b</sup> Considered positive when cocaine or metabolites benzoylecgonine or cocaethylene detected.  
<sup>c</sup> MDA is a metabolite of MDMA and a psychoactive compound itself.

## 4. Discussion

### 4.1. Drug use and standard urine detection tests

Urine drug testing is not routinely performed in trauma patient care, as evidenced by the National Trauma Data Bank 2016 Annual Report, where only 22.5% of patients had drug testing performed, of which 53.4% tested positive for illegal or prescription drugs [1]. It is unclear if the prescription drugs were being used as prescribed, or abused as is the case with many opioids and benzodiazepines in the United States [15]. In our patients, there was a 14.3% UDOA screen rate, of which 76.9% tested positive. Testing all trauma patients with confirmatory testing revealed a more accurate figure of 46% drug positive. The difference is most likely due to treating physician selection bias, as UDOA

**Table 3**  
Detected non-stimulant drugs.

Drug	Number of cases	Drug	Number of cases
Antidepressants		Opiates and opioids	
Doxepin	7	Methadone	13
Amitriptyline	5	Morphine <sup>a,b</sup>	6
Trazodone	3	Hydrocodone	5
Citalopram	1	Heroin <sup>a</sup>	3
Paroxetine	1	Codeine <sup>a</sup>	2
Antihistamines		Fentanyl	2
Diphenhydramine	12	Nalorphine	2
Doxylamine	1	Meperidine	1
Hydroxyzine	1	Oxycodone	1
Benzodiazepines and atypical benzodiazepines		Tramadol	1
Zolpidem	10	Other	
Medazepam <sup>a</sup>	5	Gabapentin	6
Clonazepam <sup>a</sup>	2	Carisoprodol	3
Diazepam <sup>a</sup>	2	Methohexital	2
Midazolam	2	Dextromethorphan	1
Alprazolam <sup>a</sup>	1		
Chlordiazepoxide <sup>a</sup>	1		
Flurazepam <sup>a</sup>	1		
Oxazepam <sup>a</sup>	1		

<sup>a</sup> Routinely detected on standard hospital urine drug of abuse screening tests.  
<sup>b</sup> Morphine is both a parent compound and metabolite of codeine and heroin.

**Table 4**  
Serum drug confirmatory testing according to mechanism.

Injury mechanism	n	Positive testing n (%)	Stimulant n (%)	Amphetamine <sup>a</sup> n (%)	Non-amphetamine stimulant n (%)	Opioid n (%)	Benzodiazepine <sup>b</sup> n (%)	Antidepressant n (%)
Penetrating	88	47 (53.4)	35 (39.8)	18 (20.5)	25 (28.4)	7 (8.0)	12 (13.6)	2 (2.3)
Gunshot wound	29	11 (37.9)	6 (20.7)	4 (13.8)	3 (10.3)	2 (6.9)	4 (13.8)	–
Stab wound	59	36 (61.0)	29 (49.2)	14 (23.7)	22 (37.3)	5 (8.5)	8 (13.6)	2 (3.4)
Blunt	184	78 (42.4)	32 (17.4)	19 (10.3)	16 (8.7)	26 (14.1)	9 (4.9)	16 (8.7)
Motor vehicle collision	48	15 (31.3)	5 (10.4)	3 (6.3)	3 (6.3)	5 (10.4)	3 (6.3)	3 (6.3)
Motorcycle collision	27	13 (48.2)	7 (25.9)	3 (11.1)	4 (14.8)	4 (14.8)	1 (3.7)	2 (7.4)
Ground level fall	57	21 (36.8)	8 (14.0)	6 (10.5)	2 (3.5)	10 (17.5)	3 (5.3)	1 (1.8)
Fall from height	50	29 (58.0)	12 (24.0)	7 (14.0)	7 (14.0)	7 (14.0)	2 (4.0)	10 (20.0)

<sup>a</sup> Amphetamines include all stimulants in Table 2 except Cocaine, BZP, and PCP, which are non-amphetamine derivative stimulant drugs.

<sup>b</sup> Includes both typical and atypical benzodiazepines as listed in Table 3.

screens were likely only ordered on patients thought to be taking illicit drugs.

This study definitively shows the presence of multiple drugs in patients with all mechanisms of traumatic injury, which would not be detected by standard hospital urine tests. One of the difficulties in researching the relationship of drugs to trauma is the sheer number of new drugs available on the market, most of which would not be detected by a standard UDOA. This is especially true for designer drugs or novel psychoactive substances (NPS), which are evolving at a rapid rate due to synthesis and marketing of synthetic cannabinoids ('spice'), synthetic cathinones ('bath salts'), substituted amphetamines, novel arylcyclohexylamines (PCP analogs), and designer opioids (fentanyl analogs) [16,17]. This study was not designed to detect any synthetic cannabinoids or most synthetic cathinones but we detected a synthetic cathinone (mephedrone) and multiple phenethylamines/amphetamines (2C-T-2, 2C-T-7, BDB [1,3-benzodioxylbutanamine], 3,4-DMA [3,4-dimethoxyamphetamine], DOEt [2,5-dimethoxy-4-ethylamphetamine], MDA [3,4-methylenedioxyamphetamine], MDMA). Part of the allure of these drugs is that they provide a different type of high, may be more inexpensive than alternatives, more readily available, and easily accessible as most are not scheduled substances. Moreover, many are known by users to be undetected by standard workplace urine drug testing, which surely contributes to their popularity [18,19]. The most commonly detected amphetamines in this study, MDMA (Ecstasy, Molly) and MDA (standalone drug and an active metabolite of MDMA), do not reliably result in a positive UDOA amphetamine screen. MDMA is not detected on many hospital standard urine drug tests until it reaches very high levels. This may be due to actual toxicity or simply due to the drug concentrating in the urine and can't be used to judge what is toxic and what isn't. Unfortunately, this is not informative for many trauma patients, whose behavior may be due to the influence of a drug but are not necessarily poisoned by it. As the above drugs become more popular, others' popularity has waned with time. Phencyclidine (PCP) is one such drug, whose usage has decreased to the point where there may be more false positives than true positives, due to common over the counter

medications such as dextromethorphan cross-reacting with the test. As such, many hospital laboratories do not include it in the routine UDOA anymore.

Opioid abuse has reached epidemic proportions in the US, resulting in a record 33,091 deaths, almost as many as the 36,161 motor vehicle traffic deaths in 2015 [20,21]. Their contribution to traumatic injury is difficult to ascertain without knowing a patient's chronic use patterns, prescriptions from all their providers, illicit use, and type of opioid consumed. In most hospital UDOAs, as in our case, the classical opiates heroin, morphine, and codeine are reliably detected. Semisynthetic opioids such as hydrocodone and hydromorphone are occasionally detected, depending on the assay used. Oxycodone and oxymorphone are less reliably detected and often require a specialized test, which some hospitals are now including in routine UDOA testing due to their usage prevalence. Synthetic opioids such as methadone, fentanyl, meperidine, tramadol, and fentanyl analogs are never detected on routine UDOA screening and always require specific tests. In our study cohort, the opioid most commonly detected was methadone, which is not detected on a routine UDOA. Hospital testing protocols vary, and providers should become familiar with their institutions UDOA to know what is and what isn't included in their screening test.

Confirmatory serum testing with LC-MS/TOF, as performed in this study, remove all doubts of what drugs are truly used by patients. At present, this testing modality is not available at most hospitals and in the few inpatient clinical laboratories who have the facilities, they are not routinely performed on a STAT basis to guide ED treatment. When available, the cost may be 3–4 times that of UDOA tests, which is a significant limitation to standard use of this test. However, we believe these tests may be useful for EDs in regional trauma centers to have a clear understanding of the drug use habits of their patient population, and on a larger scale to begin to define the relationship of different drugs to traumatic injury. Many studies examining drug use in trauma patients group all drug screens together as a general positive and compare these patients to those with negative testing [22,23]. Sedative drugs, stimulant drugs, hallucinogens, and others have completely different profiles in patterns of use and effects, with even significant variability within the classes. With confirmatory testing, drug variability can be addressed clearly and correct injury mechanism relationships can be

**Table 5**  
Association of injury characteristics between trauma patients with and without stimulant drugs.

	n	All stimulant drug positive				Amphetamine positive				Non-amphetamine stimulant positive			
		n (%)	Odds ratio	95% CI	p value	n (%)	Odds ratio	95% CI	p value	n (%)	Odds ratio	95% CI	p value
Injury type													
Non-violent	189	35 (18.5)	1	1.64–5.15	<0.001	21 (11.1)	1	1.14–4.84	0.021	18 (9.5)	1	1.97–7.88	<0.001
Violent	83	33 (39.8)	2.9			16 (19.3)	2.3			23 (27.7)	3.9		
Injury mechanism													
Blunt	184	32 (17.4)	1	1.86–5.82	<0.001	19 (10.3)	1	1.35–5.68	0.005	16 (8.7)	1	2.26–9.22	<0.001
Penetrating	88	36 (40.9)	3.3			18 (20.5)	2.8			25 (28.4)	4.6		



**Table 6**Association of injury characteristics between trauma patients with and without evidence of tobacco smoking.<sup>a</sup>

	n	COT+, n (%)	Odds ratio	95% CI	p value
<b>Injury type</b>					
Non-violent	189	68 (36.0)	1	2.25–6.77	<0.001
Violent	83	57 (68.7)	3.9		
<b>Injury mechanism</b>					
Blunt	184	65 (35.3)	1	2.40–7.14	<0.001
Penetrating	88	61 (69.3)	4.14		

<sup>a</sup> Serum cotinine (COT) used as an indicator of tobacco smoking.

defined. Although drug testing of any type may not affect immediate patient care, their utility lies in the understanding of trauma injury as a whole.

#### 4.2. Traumatic injury and stimulant drugs

Stimulant drugs were associated with more violent injury type and penetrating injury mechanism in our study cohort. This relationship persisted when stratified into amphetamine related drugs and non-amphetamine drugs, the latter of which was primarily cocaine. The link between cocaine use and firearm related homicides was established after examinations of homicide victims in Atlanta and New York City [6,7]. In homicide deaths in Fulton County, (Atlanta) Georgia in 1989, 40% of homicide victims had evidence of cocaine use [6]. African-Americans and those who were victims of firearm injuries had a higher proportion of positive cocaine tests than other races and mechanisms of death. A subsequent study out of New York City examined all homicides from 1990 to 91. They found that young African-American and Latino men were not only more likely to be victims of firearm-related homicide, but to be positive for cocaine metabolites than other groups [7]. Further studies have demonstrated that cocaine positive urine drug tests in trauma patients have been strongly associated with patients who were victims of violence [9,24]. PCP is not as popular as it once was, but in its heyday in the 1970's and 1980's there was a distinct association with violence. One of the only recent studies, a retrospective analysis of autopsy cases from the New York City Medical Examiner's office, demonstrated PCP in the blood of 138 cases. 80 of these were violent deaths, similar in proportion to other postmortem studies [12].

When examining the literature to date, the connection between methamphetamine (Meth), the most widely abused amphetamine, and violent trauma is much less clear. One review article pointed out the lack of large-scale epidemiologic studies and peer reviewed quantitative research regarding Meth use and injury [25]. Their review concluded that one of the most common causes of injury associated with Meth use is violence, especially domestic violence. A case control study comparing inmates imprisoned for murder or manslaughter and a general sample of US adults showed an association between Meth and homicide [26]. A study from Hawaii examining 4932 trauma inpatients showed that Meth patients were more likely to present with violent mechanisms of trauma such as self-inflicted injury, assault, stab wounds and gunshot wounds [10]. Other studies have shown that Meth patients present with blunt mechanisms of trauma similar to that seen with ethanol-intoxicated patients [27]. In our study, we did not have enough Meth positive cases to analyze for that drug only, but when all the amphetamine derivative drugs were grouped together there was a clear predilection for violent injury type and penetrating injury mechanism.

No other trauma study to date has systematically analyzed any of the designer drugs, or novel psychoactive substances (NPS), detected in our study. Designer drugs is a general term referring to drugs that are not naturally found and are synthesized by chemists to evade existing drug laws. They are often structural or functional analogues of already

existing drugs and novel compounds are continuously being manufactured [28]. The stimulant designer drugs detected in this study were all in the amphetamine family. One of the oldest designer drugs, MDMA, has not been linked with any violent behavior until very recently. In an ethnographic study, young men in Oakland, CA described that it gave them the confidence to enter into dangerous and violent situations that they normally wouldn't [29]. From 2000 to 2010, the majority of MDMA positive autopsy cases in San Francisco were young African-American men who died from homicide due to firearm injury [30]. Other novel psychoactive drugs such as synthetic cathinones have been anecdotally associated with violent bizarre behavior, both self-inflicted and inflicted on others [31]. Since these drugs have not been studied in trauma patients in a dedicated fashion, it is unclear what their prevalence is in those with blunt mechanisms of injury such as motor vehicle collisions and falls.

#### 4.3. Traumatic injury and non-stimulant drugs

Statistical analysis was not performed on the specific classes of non-stimulant drugs due to small sample size and the difficulty of drawing conclusions from possibly legally-obtained medications. The pattern observed however, points to opiates/opioids and antidepressants being present in more blunt mechanisms of trauma and benzodiazepines in more penetrating mechanisms of trauma. In the few prior studies, opiates have been independently associated with nonviolent injury and burns, as well as violent trauma [9,24]. Benzodiazepines have been associated with hip fractures and motor vehicle collisions in the elderly [32,33].

#### 4.4. Traumatic injury and tobacco use

Tobacco use, identified via confirmation of a major metabolite, cotinine, was associated with violent and penetrating mechanisms of trauma. Prior studies have shown an increased risk of acute lung injury in severe blunt trauma patients who were smokers or had moderate to high passive exposures [34]. There is a clear association between smoking and injury, with one study showing an injury relative risk (RR) of 1.61 (95% confidence interval (CI) 1.44 to 1.81) over non-smokers [35]. A large cohort study examining male smokers in Taiwan demonstrated that smokers had more motor vehicle collisions and a significant response between the number of cigarettes smoked per day and risk of death [36]. Smokers are 1.5 times more likely than nonsmokers to have a motor vehicle collision and 2 times as likely to have other injuries [37]. The link between cigarette smoking and injury may be due to distractibility, smoking-related diseases such as cataracts impairing vision, use of co-ingestants such as alcohol and drugs, and personality or behavioral characteristics [37]. Some studies, which are consistent with our observations, show that smokers tend to act out hostility and engage in risk taking activities more than their nonsmoker counterparts [37].

### 5. Limitations

Our study was designed to determine what drugs are truly present in trauma patients and if there is any association to mechanism of injury and injury type. Our study was not designed to determine causality. The retrospective collection of patient characteristic and disposition data may be a study limitation, although every effort was made to abstract this data accurately. Furthermore, due to the limited scope of this study, there are no outcomes or length of stay data, and so we are unable to draw any conclusions regarding severity of outcomes in relation to drug use. Another limitation is recruiting non-consecutive patients, due to the limited availability of research assistants. However, since the recruitment days were completely random, including weekdays, weekends, and evenings, we believe the study cohort represents an accurate trauma patient population at our institution. Some of the non-

stimulant drugs detected in this study are common over-the-counter or prescription medications. Since home medication information (prescription and over the counter) was abstracted from the patient charts from a single visit, we relied on the treating providers to document this information. For this reason, we did not think doing statistical analysis on opioids, benzodiazepines, antidepressants, and other non-stimulant drugs would be reliable, since most of these are likely prescription medications that were not documented on the hospital chart. Lastly, our testing protocols did not include testing for blood alcohol, marijuana, synthetic cannabinoids, antipsychotics, and other prescription medications, which may impair thought or physical activity. Future studies with comprehensive drug testing on trauma patients should prospectively collect home medication use details from patients, examine outcome data, and test patients for other substances as listed above. Asking patients questions about their social habits and details of the traumatic event would also aid in elucidating causality.

## 6. Conclusions

Our study finds that standard urine drug of abuse testing does not detect many drugs of abuse present in trauma patients. Stimulant drugs and tobacco use, indicators of multidimensional hazardous behaviors, are associated with more violent and penetrating mechanisms of traumatic injury. Stimulant drugs may directly promote aggression and violence. The clinical implication is to consider the possibility of stimulant abuse and related complications in trauma victims. Such complications could include social obstacles, unexplained hypertension and tachycardia acutely, impaired wound healing after surgery, and stimulant withdrawal symptoms during the course of hospitalization. Cigarette smoking is also associated with a substantially higher risk of trauma-related ARDS. Clinical laboratories should consider implementing assays to detect a broad range of stimulant drugs. Physicians should be alerted to the presence of novel drugs of abuse that may contribute to a patient's lifestyle choices that are not routinely detected on standard hospital urine drug testing.

## Author contributions statement

PA contributed to study design, data collection, data analysis, data interpretation, writing, and editing final manuscript. ZE and NG contributed to data collection and editing final manuscript. RD contributed to data analysis, data interpretation, and editing final manuscript. NB contributed to study design, data interpretation, writing, and editing final manuscript. RRG contributed to study design, data collection, data analysis, data interpretation, and editing final manuscript. PA takes responsibility for the paper as a whole.

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