



## High on drugs: Multi-institutional pilot study examining the effects of substance use on acute pain management

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### ABSTRACT

**Introduction:** Substance use and abuse may have the significant, but unanticipated, consequence of lessening the efficacy of opioid analgesics for acute pain management. We hypothesized that pre-injury substance use increases opioid analgesic consumption following traumatic injury.

**Methods:** This retrospective multi-institutional pilot study included admitted patients to four level 1 trauma centers with vehicular trauma over four months (n = 176). We examined the effect of positive urine drug screen (UDS; 7-drug panel, examined individually and combined, yes/no) and positive blood alcohol content (BAC,  $\geq 80$  mg/dL) on pain management with opioid analgesics over the hospital stay. Average daily opioid consumption was examined using a repeated measures mixed model, by positive UDS and BAC findings, adjusting for age, injury severity score, and non-opioid analgesia. Opioid analgesics were converted to milligram morphine equivalents (MME) and analyzed with a square-root transformation due to non-normality.

**Results:** A positive drug or alcohol test was reported in 33.5% (59/176), including 12.5% (n = 22) with positive UDS and 26% (n = 45) with a positive BAC. There were no differences in gender, injury severity scores, Glasgow coma scores, or cause of vehicular trauma between substance users and non-users; only age was significantly different. Patients with a positive UDS consumed significantly more opioids compared to those with a negative UDS (34.7 MME vs. 24.7 MME,  $p = 0.04$ ), after adjustment. Individually, detection of opiates, THC, cocaine, and amphetamines were associated with increased opioid consumption compared to their UDS negative counterparts; on the other hand, benzodiazepines and alcohol intoxication were associated with reduced opioid consumption during the course of hospitalization. However, none of the individual UDS results reached statistical significance. The largest effect of all the individual drugs was with opiates, which was associated with a borderline significant increase in opioid analgesic consumption ( $p = 0.06$ ).

**Conclusions:** Our preliminary data suggest drug use may significantly alter acute pain management following traumatic injury, corresponding to 40% increase in opioid analgesia for substance users than non-users. These results may have broad reaching implications because of the high prevalence of substance use in the trauma population.

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### Introduction

Drugs and alcohol have immediate effects on the physiological functioning and emergency assessment of trauma patients, as well

as subacute effects on treatment and development of complications [1]. The effects of drugs and alcohol on acute pain management are not well studied. Most previous work has focused comparing opioid-tolerant and opioid-naïve populations

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with non-traumatic injuries, such as cancer patients [2], those requiring knee arthroplasty [3] or other urologic, gynecologic, orthopedic and general surgical procedures [4]. In these populations, opioid users required more opioid analgesia during the perioperative period than opioid-naïve patients. Neighbor and colleagues evaluated pain intensity in the ED at triage following traumatic injury and reported that substance users reported greater pain scores than non-substance abusers, but they were equally likely to receive opioid analgesia at triage [5]. Our previous work identified an association between chronic pre-injury use of marijuana and the need for increased analgesia following motor vehicle crash (MVC) injury [6].

This study sought to examine the extent, if any, to which substance use, as identified by a positive urine drug screen (UDS) test or positive blood alcohol content (BAC) test, affects acute pain management following traumatic injury. The specific aims were to describe the effect of substance use on opioid analgesic pain management following traumatic injury, and to describe the effect of substance use on self-reported pain.

## Patients and methods

### Population and setting

This retrospective pilot study included all admitted patients to four community-based Level I trauma centers with vehicular trauma from 1/1/2016–4/31/2016 ( $n=253$ ); we excluded patients without a UDS ( $n=62$ ) and patients with length of stay  $>14$  days ( $n=23$ ) to exclude the possibility that the amount of opioids received for pain management over several weeks might lead to acute tolerance. Approval was obtained from the local institutional review board with a waiver of informed consent.

### Outcomes and covariates

The following variables were abstracted from the trauma registry (Traumabase, CDM), a database collected per State requirements for reporting, quality improvement, and quality assurance: admission date and time; toxicology drug test done (Y/N); toxicology drug test results (positive, negative, not tested); age in years; gender (M/F); detailed cause of injury (motorcycle, motor vehicle driver, etc.); Injury Severity Score (ISS); admission Glasgow Coma Score (GCS); in-hospital mortality, ICU LOS in days; hospital LOS in days.

The following variables were extracted from patient Electronic Medical Records (EMRs): specific toxicology drug test findings including blood alcohol levels and the presence/absence of other drugs of abuse identified on UDS; information on illegal and licit substance use obtained from patient history and via Screening, Brief Intervention, and Referral to Treatment (SBIRT) screening practice; all recorded pain scores throughout the hospitalization, recorded as date, time, and score (pain numeric rating scale [NRS], 0–10 scale); all recorded analgesics consumed throughout the hospitalization, recorded as the date and time, dose, and route of administration.

Substance use was defined as a positive UDS result or a positive BAC  $\geq 80$  mg/dL during routine testing. The UDS test is a multi-drug urine toxicology screen panel for tetrahydrocannabinol (THC, marijuana), amphetamines, barbiturates, cocaine, benzodiazepines, PCP, and opiates.

Patients rated their pain on the pain NRS, from 0 (no pain) to 10 (worst pain imaginable), every time a pain medication was given and when pain medication orders were adjusted. Pain medication orders are similar in the ICU and on the floor.

Analgesics were classified as opioids and non-opioids. Opioids were converted to milligram morphine equivalents (MME) using

an equianalgesic conversion. First, the total amount of each opioid was calculated for each 24-hour period, and this was converted to MMEs by multiplying the dose for each opioid by the conversion factor, and then they MMEs were summed. There are available conversion charts to determine the equivalency factor; this study utilized the chart provided in a CDC guideline [7].

The number of doses of non-opioids received was coded as the total number of non-opioids prescribed each day, e.g. if a patient received 500 mg acetaminophen twice daily, the amount of non-opioids was coded as two. This amount was used for adjustment purposes in the final model.

### Statistical analysis

SAS version 9.4 was used for analysis (SAS®, Cary, NC). Statistical significance was  $p < 0.05$ .

All opioids consumed from hospital admission through discharge were used to calculate total daily opioid consumption, which was the sum of opioids consumed for each 24-hour period. Total daily opioid use was examined using a repeated measures general linear mixed model to test the hypothesis that prior substance use was associated with greater consumption of opioid analgesia during the course of the hospital stay. The final model utilized a square-root transformation due to non-normality of daily opioid use and followed a gaussian distribution. The model used a compound symmetry covariance structure and included covariates of ISS, age, and the amount of non-opioid used daily. Time was modeled as day (24-hour period); there was no time interaction.

Pain scores reported during the entire hospital stay were used to calculate an average daily pain score for each 24-hour period. This average daily pain score was examined with a repeated measures general linear model to test the hypothesis that prior substance use was associated with higher pain scores. The final model for pain scores utilized a compound symmetry covariance structure and included covariates of age, ISS, daily MME consumption, and daily non-opioid analgesia consumption. Time was modeled as day (24-hour period). There was no time interaction.

The effect of a positive UDS (any of seven drugs on a 7-drug panel, individually and combined (yes/no)) and positive BAC ( $\geq 80$  mg/dL) on pain scores and opioid analgesic consumption were examined with separate repeated measures general linear mixed models – for instance, benzodiazepine use was dummy coded as positive UDS for benzodiazepine vs. negative UDS for benzodiazepine. Multi-collinearity was not examined, as each drug was tested in separate models. We examined each drug individually to aid in the clinical interpretation of what effect a specific drug may have on narcotic usage and pain scores, rather than modeling all drugs together and determining how each individual drug differs from the presence of any drug. Too few patients tested positive for PCP ( $n=1$ ), and barbiturates ( $n=0$ ), and these drug findings were not analyzed.

We also examined the effects of substance use on patient demographics, injury characteristics, and clinical outcomes with Chi-square and Wilcoxon rank-sum tests.

## Results

The pilot study included 176 patients with motor vehicle crash: 78% were motor vehicle occupants, 12% pedestrians, and 10% motorcyclists. The median (IQR) age of the population was 38 (24–56) years, 64% were male, with a median ISS of 9 (5–14). The majority (79%) of patients had no neurologic impairment.

A positive drug or alcohol finding was reported in 33.5% (59/176), including 12.5% ( $n=22$ ) with a positive UDS for drugs and 26%

(n = 45) with a positive BAC (Table 1); eight patients were positive for both UDS and BAC. Most patients (64%) with positive UDS for drugs reported multi-drug use. The most commonly found drug was THC (n = 13), followed by opiates (n = 10), amphetamines (n = 10), benzodiazepines (n = 9), and cocaine (n = 3).

Patients with a positive UDS or positive BAC were significantly younger than patients that tested negative for drugs and alcohol (Table 1). There were no other differences in patient characteristics/outcomes by substance abuse status (Table 1).

### Opioid use

The majority of analgesics prescribed were opioids (81%). Nearly all patients (95%) received opioid analgesics; 64 (42%) patients received only opioid analgesics and no non-narcotic analgesics were prescribed. The median daily MME was 21 mg, and the average daily non-opioid count was 1.1.

In Fig. 1, median MME (mg) consumption is presented for the first 24 h and throughout the hospitalization, by substance use status. MME was greatest in patients testing positive for opiates. The lowest opioid consumption was reported for patients with positive UDS for benzodiazepines. The median MME was higher during the first 24 h compared to the entire hospital length of stay.

After adjustment for age, ISS, and daily non-opioid use, the results of the repeated measures mixed model demonstrated significantly greater opioid consumption, compared to patients with a negative UDS, in patients testing positive for drugs (34.7 MME vs. 24.7 MME,  $p = 0.04$ ), corresponding to a 1.4-fold increased consumption of opioids for acute pain management.

Individually, detection of opiates, THC, cocaine, and amphetamines on UDS were associated with increased opioid consumption compared to their UDS negative counterparts, after adjustment (Table 2). On the other hand, benzodiazepine use and alcohol intoxication were associated with reduced opioid

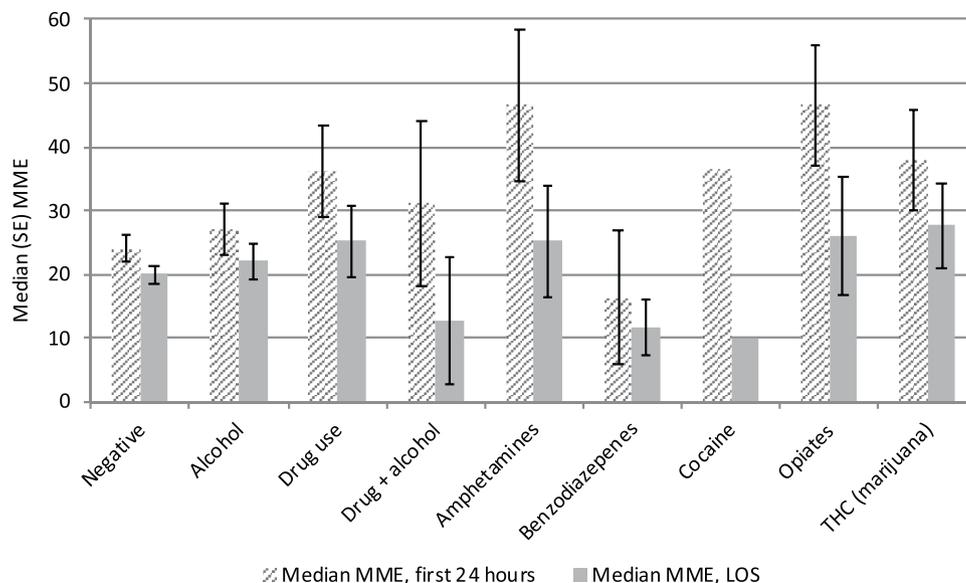
**Table 1**  
Characteristics/clinical outcomes, by substance use.

Characteristic, n (%)	+UDS (n=22)	+BAC (n=45)	-UDS and -BAC (n=117)	p value**
Male sex	14 (63.6%)	28 (62.2%)	75 (64.1%)	0.97
Age, years	28 (24-43)	31 (23-47)	44 (25-61)	<b>0.01</b>
Cause				0.78
Motor vehicle occupant	17 (77.3%)	34 (75.6%)	93 (79.5%)	
Motorcyclist	2 (9.1%)	5 (11.1%)	14 (12.0%)	
Pedestrian	3 (13.6%)	6 (13.3%)	10 (8.6%)	
GCS 13-15	20 (95.2%)	41 (95.4%)	112 (93.3%)	1.00
Injury severity score (ISS)				0.36
ISS < 16	16 (72.7%)	35 (77.8%)	90 (76.9%)	
ISS 16-24	6 (27.3%)	6 (13.3%)	14 (12.0%)	
ISS > 24	0 (0%)	4 (8.9%)	13 (11.1%)	
Outcome				
Mortality	0 (0%)	1 (2.2%)	3 (2.6%)	1.00
ICU admission	19 (86.4%)	36 (80.0%)	83 (70.9%)	0.08
LOS, days*	2 (2-6)	2 (1-4)	3 (1-5)	0.41
ICU LOS, days*	2 (1-4)	1 (0-4)	2 (0-3)	0.68

UDS, urine drug screen; BAC, blood alcohol content; GCS, Glasgow coma score.

\* median (IQR).

\*\* P values reported using Pearson chi-square and Wilcoxon rank-sum tests, comparing positive UDS or BAC (n = 59) vs. negative UDS and BAC (n = 117).



**Fig. 1.** Median (standard error) morphine milligram equivalents (MME) during the first 24 h and throughout the hospitalization, by urine drug screen and alcohol content results.

**Table 2**

Adjusted average daily opioid analgesic requirements (morphine milligram equivalents, MME) throughout the hospitalization.

Urine drug screen (UDS) finding	UDS positive		UDS negative		P value
	N	Average MME	N	Average MME	
Drug use	22	34.7	154	24.7	<b>0.04</b>
BAC $\geq$ 80 mg/dl	45	24.2	131	26.3	0.59
Drug use + BAC $\geq$ 80	8	30.9	168	25.6	0.48
Amphetamines	10	30.8	166	25.5	0.45
Benzodiazepines	7	19.4	169	26.0	0.50
Cocaine	3	29.0	173	25.7	0.79
Opiates	9	37.9	167	25.1	0.06
THC (marijuana)	13	31.7	163	25.4	0.33

BAC, blood alcohol content. Average daily MME was analyzed with a repeated measures general linear mixed model and reported as least square means, adjusting for age, injury severity score, and daily non-opioid analgesia.

consumption during the course of hospitalization. However, none of these associations reached statistical significance. The largest effect of all the individual drugs was with opiates, which was associated with a borderline significant increase in opioid analgesic consumption ( $p = 0.06$ ).

The results of the full model, including the effects of the covariates, can be found in Supplementary Table S1. Injury severity score and age were not significantly associated with total daily opioid consumption, whereas there was a significant association between increasing non-opioid analgesia with an increase in opioid consumption.

#### Pain scores

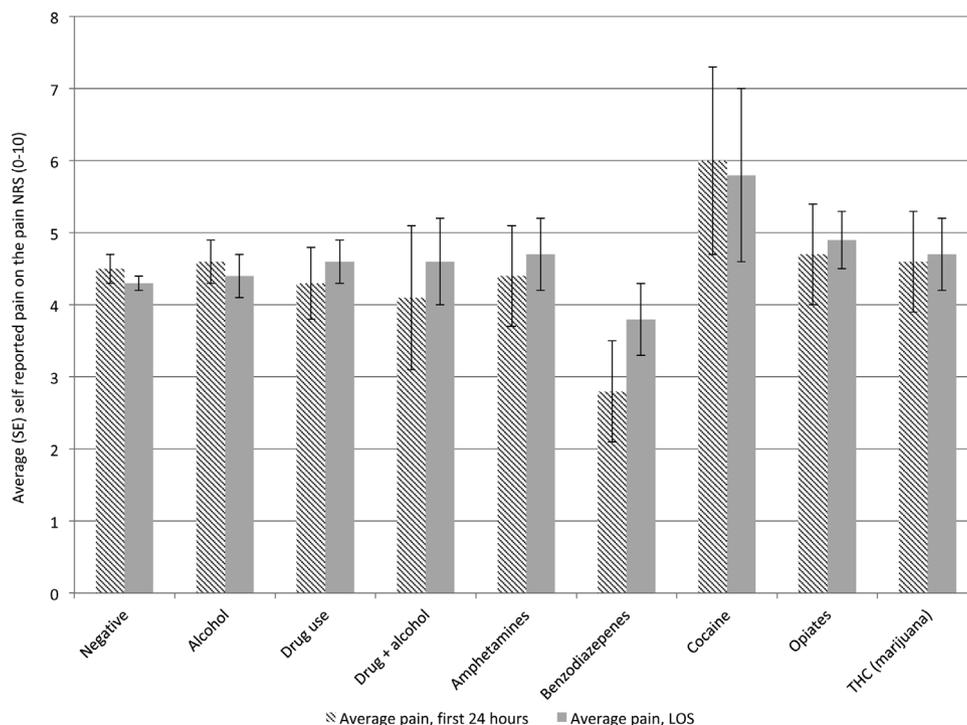
The average daily pain score was 4.9. Average pain scores were relatively consistent within a range of approximately 4–6 on a 0–10 scale within the first 24 h of arrival (Fig. 2), with the exception of patients with a positive UDS for benzodiazepines, who reported a lower average pain score. Patients with both drug use and alcohol intoxication had large variability in pain scores. A positive UDS finding for any of the examined drugs was associated with a lower

pain score during the first 24 h compared to the entire hospitalization, whereas patients who were negative for drugs/alcohol or positive for only alcohol observed the opposite effect: the pain scores during the first 24 h were higher compared to the entire hospitalization.

After adjustment, average daily pain scores were similar irrespective of UDS and BAC findings (Table 3). In other words, toxicology findings did not affect self-reported pain scores. With the exception of non-narcotic consumption, the covariates included in the models (injury severity score, age, narcotic consumption) were all significantly associated with average daily pain scores (Supplementary Table S2).

#### Non-opioid use

The effects of substance use on non-opioid analgesia can be found in Supplementary Table S3. One interesting finding was that patients with a positive UDS received, on average, fewer doses of non-narcotic analgesia than patients who were UDS negative (0.5 vs. 1.2,  $p = 0.01$ ), although total daily non-narcotic doses received were low in both groups.



**Fig. 2.** Average (standard error) pain numeric rating scale (NRS) scores during the first 24 h and throughout the hospitalization, by urine drug screen and alcohol content results.

**Table 3**  
Adjusted average daily pain scores using self-reported pain numeric rating scale (0–10) throughout the hospitalization.

Urine drug screen (UDS) finding	UDS positive (UDS+)		UDS negative (UDS-)		P value
	N	Average pain	N	Average pain	
Drug use	22	4.6	154	4.4	0.42
BAC $\geq$ 80 mg/dl	45	4.4	131	4.4	0.87
Drug use + BAC $\geq$ 80	8	4.6	171	4.4	0.76
Amphetamines	10	4.9	166	4.4	0.34
Benzodiazepines	7	4.4	169	4.4	0.99
Cocaine	3	5.6	173	4.4	0.20
Opiates	9	4.6	167	4.4	0.63
THC (marijuana)	13	4.7	163	4.4	0.55

BAC, blood alcohol content. Average daily pain scores were analyzed with a repeated measures general linear mixed model and reported as least square means, adjusting for age, injury severity score, and daily total non-opioid analgesia and opioid analgesia (milligram morphine equivalents).

## Discussion

These preliminary data suggest that patients with a positive UDS have greater consumption of opioids compared to drug-naïve patients. Overall mean pain scores were fairly consistent in the moderate range irrespective of the patient's pre-injury drug use pattern, yet substance users required more opioid analgesia to maintain adequate pain control compared to drug-naïve patients. The largest effect of all the individual drugs was observed in patients with opiates detected on UDS, corresponding to a 150% increased consumption of opioids for acute pain management that was borderline statistically significant. It is likely the sample size of patients testing positive for opiates was too small to demonstrate statistical significance, since the magnitude of the effect of opiates was similar to that of overall drug use.

Few published studies have sought to quantitatively analyze substance use status and acute pain management in the perioperative setting. In 1993 de Leon-Casasola and colleagues studied perioperative analgesia in cancer patients, demonstrating daily epidural and intravenous morphine requirements were two- to three-fold greater in opioid users ( $n=17$ ) compared to opioid-naïve patients ( $n=99$ ) [2]. Rapp et al. performed a case-control study and reported greater requirement for opioids through patient-controlled analgesia for opioid tolerant patients when undergoing urologic, gynecologic, orthopedic and general surgical procedures [4]. More recently Patanwala et al. examined post-surgical analgesic response to opioids following total knee arthroplasty for opioid tolerant vs. opioid-naïve patients [3]. Among 29 patients evaluated during the perioperative period, there was a significant increase in opioid consumption and greater pain NRS scores immediately after surgery in the opioid tolerant patients relative to the naïve group. Neighbor and colleagues did not report opioid consumption in their study of trauma patients but demonstrated greater pain intensity in the ED at triage for substance users vs. non-substance users [5]. Our study identified greater opioid consumption to maintain similar pain intensity for substance users vs. non-substance users, which may, in part, be driven by the patients who tested positive for opiates.

Alcohol intoxication did not have an effect on opioid consumption or pain scores in our study. A review of the effect of alcohol use on pain management following trauma provided evidence that alcohol intoxication has short term pain inhibitory effects, yet, chronic alcohol users experience hyperanalgesia with abstinence and withdrawal [8,9]. Our study did not collect information on the presence of an alcohol abuse disorder, which appears to be an important confounding variable worth examining in future studies.

The findings of this study have two potential implications. The first implication extends to substance use testing following trauma. Only a small proportion of trauma patients are tested

for substance use despite the well-established association between substance abuse and injury. A study of nearly one million trauma admissions from the National Trauma Data Bank reported that only 36% tested for drug use [10]. Drug testing in the elderly may be even more underutilized but as potentially significant: drug testing was performed in only 12% of elderly trauma patients, yet nearly half (48%) of those who were tested had a positive result [11]. Currently there are no guidelines on substance use testing following injury. The Centers for Disease Control and the National Center for injury Prevention and Control have jointly published guidelines for unhealthy alcohol screening and brief intervention following trauma [12], but these guidelines only apply to Level I/II trauma centers. Further, the American College of Surgeons mandates alcohol use screening for Level I/II trauma centers and brief intervention programs for Level I trauma centers only. Early identification of substance use could also be a window of opportunity for intervention [10].

A second implication for our preliminary findings supports that patients with substance use issues merit special consideration during acute pain management. It is well recognized that acute pain management is more challenging in opioid-tolerant patients [13], and may involve significant, individualized deviations from a hospital's standard pain management protocol. Our results suggest trauma patients who were UDS positive for opiates consumed more opioids for acute pain compared to those who were negative for opiates on UDS, despite the large decrease in opioid consumption that the opiate-positive patients experienced from the first 24h compared to the entire hospitalization. Special considerations include multimodal analgesia, withdrawal prevention, opioid substitution therapy and opioid rotation, and early consultation for discharge planning.

There are several limitations associated with this study. Most importantly, this was a pilot study intended to be hypothesis generating. The results of this study, while intriguing, require a larger, prospective study to confirm that substance use result in greater opioid consumption following injury. The study was only 60% powered to detect the differences observed in this study and would require 294 patients in a prospective study. Second, we categorically identified substance users as those with a positive UDS, which identifies patients who have drugs present at the time of admission. There may be patients who are misclassified as substance users who received opioids or other drugs en route, prior to hospital admission, and there may be patients who are misclassified as non-substance users who regularly use drugs prior to injury but had a negative UDS. For instance, of the 120 patients who we categorized as being drug-naïve based on UDS, 3 (2.5%) self-reported as being a substance user. Another 20 patients with negative UDS self-reported at least occasional use of marijuana. However, there was a large amount (49%) of missing self-reported drug use information, so it was not included in the

definition of a substance use. Third, this study enrolled patients who may be cognitively impaired including those who are mechanically ventilated and sedated. Patients who are conscious but non-verbal will use the picture face scale instead of the pain numeric rating scale. This scale also utilizes a pain NRS but there are fewer categories: 0 (no pain), 2 (just a little bit) 4 (hurts a little more), 6 (hurts even more), 8 (hurts a whole lot), and 10 (hurts as much as you can imagine). Only the anchor points of 0 and 10 are directly comparable to the pain NRS (0–10). Finally, these results may not be generalizable to non MVC injuries.

### Conclusions

These preliminary data suggest that substance use may significantly alter acute pain management following traumatic injury. These results may have broad reaching impact because substance abuse is on the rise, thus greater numbers of patients with positive drug and alcohol abuse histories are likely to present at the nation's trauma centers.

### Authors' contributions

Ms. Salottolo is responsible for literature search, design, data acquisition, data analysis, interpretation of data, and drafting the manuscript. Drs. McGuire and Peck are responsible for study conception, literature search, interpretation of the data, and critical revisions. Drs. Mains, Madayag and Tanner are responsible for interpretation of the data and critical revisions. Dr. Bar-Or is responsible for interpretation of the data and drafting the manuscript. All authors provided final approval of the submitted manuscript.

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### Ethics approval and consent to participate

The study was approved from the Institutional Review Boards at each respective facility; informed consent was waived. Reference numbers: Swedish Medical Center: 987891; St. Anthony Hospital: 973145; Penrose Hospital: 975740; Medical City Plano: 103099.

### Competing interests

All authors declare there are no conflicts of interest.

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### Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.injury.2019.01.003>.

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