## Title

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# Opioid and Benzodiazepine Withdrawal Syndromes in Trauma ICU Patients: A Prospective Exploratory Study

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**Objectives:** Trauma ICU patients may require high and/or prolonged doses of opioids and/or benzodiazepines as part of their treatment. These medications may contribute to drug physical dependence, a response manifested by withdrawal syndrome. We aimed to identify risk factors, symptoms, and clinical variables associated with probable withdrawal syndrome.

**Design:** Prospective exploratory observational study.

**Setting:** Trauma ICU in large medical center in Puerto Rico.

**Participants:** Fifty patients who received opioids and/or benzodiazepines for greater than or equal to 5 days.

**Measurements and Main Results:** Using an opioid/benzodiazepine withdrawal syndrome checklist developed from research in adult ICU patients, the Diagnostic and Statistical Manual of Mental Disorders-5, and the *International Classification of Diseases,* 10th Edition, we evaluated patients at baseline and for 72 hours after drug weaning was initiated. Patients received opioid/benzodiazepine (88%), opioid (10%), or benzodiazepine (2%). Probable withdrawal syndrome occurred in 44%, questionable withdrawal syndrome in 20%, and no withdrawal syndrome in 18 (36%). Signs that were more frequent in the probable withdrawal syndrome group were agitation, diarrhea, fever, tachypnea, lacrimation, and hyperactive delirium. Patients who developed probable withdrawal syndrome spent almost double the amount of time receiving mechanical ventilation, and length of stay was higher in both ICU and hospital when compared with patients in the other two groups. Age, cumulative opioid dose amounts, and previous drug (opioid/benzodiazepine, cannabis, cocaine, or heroin) use were associated with odds of developing withdrawal syndrome. With the addition of Richmond Agitation-Sedation Scale and delirium to the multilevel analysis, older age no longer had its protective effect, whereas increase in Richmond Agitation-Sedation Scale scores, delirium presence, and increased duration of mechanical ventilation were associated with higher odds of withdrawal syndrome.

**Conclusions:** We identified probable withdrawal syndrome in a sample of trauma ICU patients through observation of several associated symptoms. Significant factors associated with withdrawal syndrome found in this study should be considered when caring for patients being weaned from opioids and/or benzodiazepines. Further validation of the opioid/benzodiazepine withdrawal syndrome checklist is recommended.

**Key Words:** benzodiazepines; intensive care unit; opioids; pain trauma; withdrawal syndrome

ICU patients frequently receive opioid and benzodiazepine medications to treat the pain, anxiety, and agitation experienced during a critical illness. Trauma ICU (TICU) patients may require high and/or prolonged doses of opioids to manage pain associated with multiple open wounds, fractures, painful procedures, and/or surgery. They may also require benzodiazepines to prevent or manage anxiety and agitation and to facilitate effective mechanical ventilation (MV).

Although the effect of different pain and sedative medication regimens on TICU patients is unclear, prior evidence suggests that administration of opioid and benzodiazepine medications in the ICU setting is associated with the development of many complications including delirium (1–3) and poor patient outcomes (e.g. longer days spent on MV and longer ICU and hospital stays) (4). Exposure to high or prolonged use of opioids and benzodiazepines may also contribute to both drug tolerance (increased dose of medication is required to maintain the same effect) and drug

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physical dependence (abrupt or gradual drug withdrawal causes unpleasant physical symptoms) (5, 6). Once drug dependence has developed, patients are then at risk for withdrawal syndrome (WS), a group of serious physical and psychologic symptoms that occur upon the abrupt discontinuation of these medications (6–9). The effect of WS on patient recovery and prolonged ICU stay is unclear (7, 10).

Unlike in the PICU patient population, physical dependence during drug weaning of adult ICU patients exposed to prolonged doses of opioids and benzodiazepines has received little study. Indeed, there is a large discrepancy in the amount of literature regarding WS in the adult versus PICU populations. There are two descriptive studies with retrospective chart review designs and small samples in adult ICU surgical-trauma patients (7) and burn ICU MV patients (8). Cammarano et al (7) found that 32% of their sample ($n$ = 28) developed WS after prolonged exposure to high doses of analgesics and sedatives. Brown et al (8) found that all burn MV patients ($n$ = 11) who received opioids and benzodiazepines for more than 7 days developed WS. In a prospective experimental study of major abdominal and cardiothoracic post-surgical ICU patients, 35% who received a combination of opioids and benzodiazepines ($n$ = 14) developed marked withdrawal compared with 28% who received a combination of opioids and propofol ($n$ = 15) (11). These three studies were reported more than 1 decade ago, prior to the current recommended change in sedative management (12). A recent prospective study of 54 TICU patients showed a lower occurrence (16.7%) of iatrogenic (treatment induced) opioid WS than in previous studies (10). Regarding pediatric studies, two recent reviews evaluated 23 and 33 studies, respectively, of WS done in the PICU population (13, 14).

Of note, there is no valid and reliable WS assessment tool available for the adult ICU population, although there are two tools for pediatrics. These tools are the Withdrawal Assessment Tool-1 (15) and the Sophia Observation withdrawal Symptoms-scale (16). The lack of a WS assessment tool for adult ICU patients may have contributed to the lower number of publications about WS in adults.

This difficulty in the ability for clinicians to measure adult WS is particulary relevant considering the current U.S. opioid epidemic and was one of the reasons we undertook this exploratory work. Little is known about the actual occurrence of WS, risk factors, and its consequence in adult patients. Therefore, the objectives of this exploratory study were to (1) identify risk factors associated with probable WS among adult TICU patients exposed to opioids and/or benzodiazepines; (2) explore clinical characteristics, signs and symptoms, and outcomes among patients who developed probable WS, questionable WS, and patients who did not develop WS.

## MATERIALS AND METHODS

### Study Design

We conducted a prospective exploratory observational study with repeated measures. The Institutional Review Board of the University of Puerto Rico, Medical Sciences Campus approved this study, protocol number A5580416. The study period was from September 2016 to May 2017.

### Setting and Patients

Patients 21 years or older with an admission order to TICU at the Trauma Hospital of Puerto Rico and an expected exposure to opioids and/or benzodiazepines for 5 days or more (based on the degree of illness) were screened for study eligibility. Patients who had head trauma with neurologic dysfunction, who were prisoners, and/or had alcohol use disorder by family or patient report were excluded (**Fig. 1**). Consent was obtained in patients able to consent; for those unable to provide it, a family member (next-of-kin) provided authorization for the patient's participation. When patients became capable of providing their own consent during the course of the study, they were asked about their desire to continue study participation and if the previously obtained data could be used.

### Instruments

As established earlier, currently there is no validated tool for assessing WS in adult ICU patients which is a challenge in the study of WS in this population. Other challenges are that the signs and symptoms lack specificity, and there are similarities in these WS and signs and symptoms seen in other conditions like delirium, undersedation, pain, and anticholinergic toxidrome (17, 18). This is particularly true for sign and symptoms related to CNS irritability and some nervous system activation (e.g. tachycardia, tachypnea). However, although not specific, WS has unique signs and symptoms related to gastrointestinal system dysfunction and some nervous system activation (e.g. yawning, fever, lacrimation) (17, 18).

Since we recognized the limitation of no validated assessment tool for adult ICU patients, we created a sign and symptom checklist to measure *potential* indicators of WS of opioids and/or benzodiazepines. For our checklist, we retrieved potential indicators from the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (6), the *International Classification of Diseases,* 10th Edition Classification of Mental and Behavioral Disorders (19), and previous WS research in adult ICU patients to develop the checklist (7, 8, 11). **Figure 2** depicts the signs and symptoms of opioid and/or benzodiazepine WS that were included on the checklist. Tachycardia and tachypnea were defined as more than 100 beats per minute and more than 30 breaths per minute, respectively, high blood pressure as a systolic pressure more than 150 mm Hg, and/or diastolic pressure more than 90 mm Hg. We used the Richmond Agitation-Sedation Scale (RASS) score (20) to determine level of arousal (restlessness and agitation) and the Confusion Assessment Method-ICU (CAM-ICU) (21) to determine delirium.

The DSM-5 establishes that, to identify opioid and/or benzodiazepine withdrawal, the patient must develop three or more opioid and/or two or more benzodiazepine symptoms after cessation or a reduction in opioid or benzodiazepine doses after a prolonged use (6). Withdrawal signs and symptoms may begin to appear within 6–12 hours for short-acting opioids (peak intensity 1–3 d) and 6–8 hours for benzodiazepine (peak in intensity 2 d) (6). Taking DSM-5 criteria into account and given that the checklist has not undergone a formal validation process, we developed the following categories for our patients: (1) "probable" WS: patients presenting with three

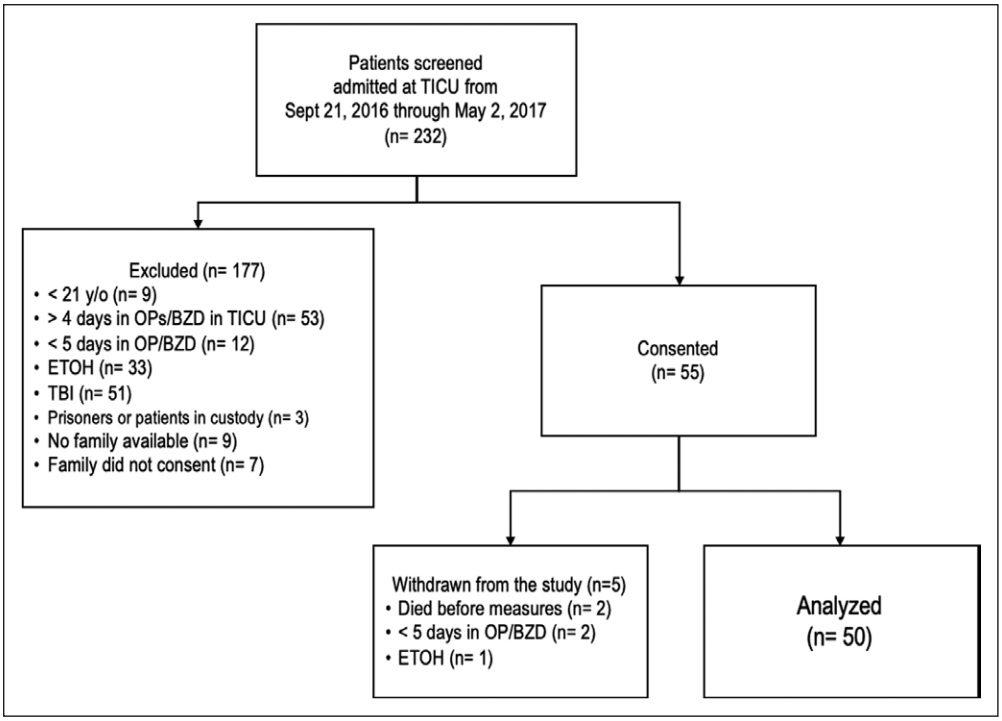


**Figure 1.** Patients recruitment flow chart. BZD = benzodiazepine, ETOH = alcohol, OP = opioid, TICU = trauma ICU, TBI = traumatic brain injury, y/o= year old.

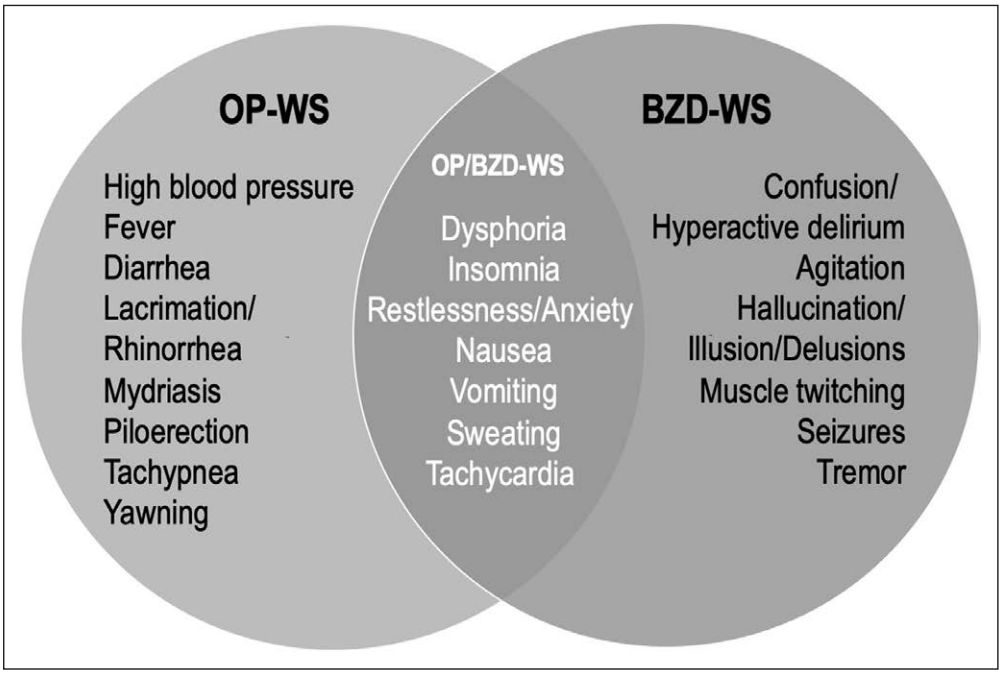


**Figure 2.** Withdrawal syndrome signs and symptoms according to medication. Signs and symptoms retrieved from American Psychiatric Association (6), Cammarano et al (7), Brown et al (8), Korak-Leiter et al (11), and World Health Organization (19). BZD = benzodiazepine, OP = opioid, WS = withdrawal syndrome.

or more sign/symptoms of opioid-WS and/or two or more sign/symptoms of benzodiazepine-WS that were not present at baseline (i.e., fourth day of opioid and/or benzodiazepine administration); (2) "no" WS: patients not presenting with the minimum sign/symptoms for opioid-WS and/or benzodiazepine-WS; and (3) "questionable" WS: patients presenting with the required number of sign/symptoms, but one or more of these were present during baseline evaluation. For example, tachycardia that was present at baseline evaluation was not counted as a probable withdrawal sign during weaning.

### Data Collection and Procedures

Recruitment and data collection were performed in TICU patients as well as patients with admission orders for TICU (i.e., those in the stabilizing unit or in the post-anesthesia care unit waiting for transfer to TICU). If study patients were transferred to the intermediate unit while data collection was ongoing in the TICU, data collection continued in this unit.

Baseline data (i.e., demographic and clinical) were obtained from the patient's clinical record or by family or patient interview. Daily and cumulative amounts of opioids (morphine IV-equivalent) (22, 23) and benzodiazepines (lorazepam IV-equivalent) (24, 25) and daily doses of other sedatives such as propofol and antipsychotics used from the arrival at Trauma Hospital and during the TICU stay were also collected. Patient days on MV, length of TICU stay, and length of hospital stay were documented.

Bedside patient assessment data using the sign and symptom checklist were collected on the fourth day of patients receiving opioids and/or benzodiazepines in order to establish baseline data. After the fourth day of receiving opioids and/or benzodiazepines, bedside patient assessment data were also collected once the start of the weaning process (i.e., intention to wean or weaning execution) for up to 72 hours after the beginning of opioid and/or benzodiazepine weaning. If weaning was stopped and the patient returned to a similar previous dose, bedside measures ceased. When the weaning process was reestablished, measures began again and continued for up to 72 hours. Data on each of the signs and symptoms were collected twice a day (between 8:00 AM and 12:00 PM and between 5:00 PM and 9:00 PM). Vital sign abnormalities from the previous 8–12 hours were recorded during each patient assessment. Due to a limited budget for this exploratory study, all data collection and assessments were performed by the first author.

### Statistical Analysis

Patient demographic and clinical data are presented as medians (interquartile range) for continuous variables and frequencies (%) for categorical variables for patients as a total group and also according to WS category (probable, questionable, no WS). To compare demographic and clinical characteristics in patients by WS category, we conducted Fisher exact test for categorical variables and Kruskal-Wallis test for continuous variables. A Bonferroni correction to adjust alpha for 13 comparisons was calculated, and a $p$ value of less than 0.004 was necessary to determine statistical significance.

A mixed-effects logistic regression was conducted to determine the contribution of demographic and clinical variables to the development of probable WS. We evaluated several candidate models for WS (probable vs no), in terms of their fit, using Akaike information criterion (AIC) and Bayesian information criterion (BIC). AIC and BIC are the most commonly used criteria for candidate model selection in regression analysis, with lower values reflecting a better fit of the candidate model to the existing data (26). McFadden's pseudo-$R^2$ (27) was also calculated, comparing each model to the null model. The predictors considered in the multivariate models were age, severity of illness measured by the Acute Physiology and Chronic Health Evaluation (APACHE) II score, cumulative dose amounts of both opioids and benzodiazepines from time of first administration to a WS assessment day, days on both opioids and benzodiazepines, history of previous drug use, duration on MV, and both length of stay in ICU and hospital. These predictors were included in the model since there have been identified as risk factors in several studies with adults and/or PICU populations cited in two recent literature reviews (13, 14). The all-inclusive model was then reduced one variable at a time to determine the best prediction model. We then included two WS signs (agitation/restlessness using the RASS score and presence of delirium) to this best prediction model to determine if the model improved its fit. Our rationale for examining these variables was that they were highly correlated with WS occurrence in a bivariate analysis. Spearman correlation coefficients were used to further explore the relation between "days on opioid treatment" and "cumulative dose of opioid" variables (predictors in the regression models).

## RESULTS

### Patient Characteristics

Two-hundred thirty-two patients admitted to TICU from September 2016 to May 2017 were screened. Fifty-five patients' family members or patients consented for the study. Of those, five withdrew from the study before all data were collected, and data from 50 patients were analyzed (Fig. 1). The majority of patients were male (88%) with a median age of 37 (27–49); 90% were mechanically ventilated and 34% used drugs (i.e., opioid, benzodiazepine, heroin, cocaine, cannabis), either illicitly or per prescription, prior to hospitalization. The median APACHE II score was 15 (13–18). Mechanism of trauma was blunt (53%), penetrating (43%), or burns (4%). Patients spent 13 days (7–17 d) in the ICU and 21 days (14–32 d) in the Trauma Hospital. The 45 patients who were mechanically ventilated spent 11 days (7–14 d) on MV.

Patients received both opioids and benzodiazepines (88%) or only opioids (10%) or benzodiazepines (2%). Patients received continuous infusions and/or intermittent doses of fentanyl (92%) and/or morphine (82%) for analgesia and midazolam (84%) and/or lorazepam (70%) for sedation. Patients received a median cumulative dose of 1,144 mg (544–2,388 mg) of opioids over 11 days (7–16 d) and 688 mg (276–1,366 mg) of benzodiazepines over 11 days (5–13 d), until the last bedside patient assessment. The daily median opioid dose was 109 mg (60–143 mg), and the daily median benzodiazepine dose was 72 mg (44–100 mg). In 50% of patients, continuous propofol was administered as a single agent or in combination with benzodiazepines. Thirteen patients (26%) and three patients (6%) received antipsychotics or neuromuscular blockers, respectively.

Probable WS occurred in 22 patients (44%), questionable WS in 10 patients (20%), and no WS in 18 patients (36%). In those patients who developed probable WS, WS occurred a median of 2 (1–3) times during the measurement period. A total of 49 events of probable WS occurred in the 22 patients.

### Differences in Signs and Symptoms Among Probable WS Patients, Questionable WS Patients, and No WS Patients

Distribution of signs and symptoms experienced by patients at any time during the study are shown in a box-grid (**Supplementary Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCX/A144), according to WS status. Compared with patients without WS, patients with probable WS had higher frequencies (≥30% differences) in presence of agitation (41% vs 11%), restlessness (91% vs 28%), diarrhea (45% vs 6%), fever (55% vs 22%), high blood pressure (73% vs 33%), lacrimation (45% vs 11%), tachypnea (55% vs 17%), and hyperactive delirium (59% vs 11%). The frequencies of these symptoms in patients with questionable WS generally fell between the estimates in the two other categories. Compared with patients with probable WS, there was a higher percentage of patients with questionable WS who had vomiting (20% vs 9%), high blood pressure (80% vs 73%), and tachycardia (100% vs 95%).

Age and APACHE score among the three patient groups were similar (**Table 1**). More patients who developed probable WS were male, had previously used drugs, were admitted with a penetrating injury, and received MV more frequently (all $p$ = not significant). Probable WS patients spent almost double the amount of time receiving MV when compared with patients in the other two groups ($p = 0.0008$). Length of stay was higher in both ICU ($p = 0.0002$) and hospital ($p = 0.0015$) for patients in the probable WS group. Although the majority of patients who developed probable WS were previous drug users (12 of those patients [85.7%], 10 of the drug naive patients [38.5%] also developed WS ($p$ = not significant). Cumulative opioid dose was significantly higher in the probable WS group when compared with the other two groups ($p = 0.001$). However, cumulative benzodiazepine dose was not significantly different among groups. The number of weaning attempts from both opioid and benzodiazepine were also similar among groups.

**TABLE 1. Differences in Demographics and Clinical Variables According to Patient Group**

| Demographic and Clinical Variables | No WS (*n* = 18) | Probable WS (*n* = 22) | Questionable WS (*n* = 10) | *p* |
|---|---|---|---|---|
| Age, median (IQR) | 35 (25–48) | 37 (29–49) | 36 (25–43) | 0.83 |
| Sex, *n* (%) | | | | 0.27 |
| Female | 4 (22) | 2 (9) | 0 (0) | |
| Male | 14 (78) | 20 (91) | 10 (100) | |
| Acute Physiology and Chronic Health Evaluation II, median (IQR) | 15 (12–19) | 15 (13–18) | 15 (14–16) | 0.84 |
| Previous drug users, *n* (%) | | | | 0.01 |
| Yes (opioid/benzodiazepine, cannabis, cocaine, or heroin) | 2 (11) | 12 (55) | 3 (30) | |
| No (drug naïve patients) | 16 (89) | 10 (45) | 7 (70) | |
| Trauma mechanism, *n* (%) | | | | 0.16 |
| Blunt | 13 (72) | 8 (36) | 5 (56) | |
| Penetrating | 5 (28) | 12 (55) | 4 (44) | |
| Burn | 0 (0) | 2 (9) | 0 (0) | |
| MV, *n* (%) | | | | 0.06 |
| Yes | 14 (78) | 22 (100) | 9 (90) | |
| No | 4 (22) | 0 (0) | 1 (10) | |
| Duration on MV, d, median (IQR) | 7.5 (4–12) | 14 (10–20) | 7 (4–9) | 0.0008[b] |
| Length of stay ICU, d, median (IQR) | 11 (5–14) | 16.5 (13–27) | 9.5 (6–12) | 0.0002[b] |
| Length of stay hospital | 13.5 (10–22) | 28 (21–47) | 18 (15–36) | 0.0015[b] |
| Cumulative opioid dose[a], median (IQR), mg | 660 (336–1,126) | 1,700 (885–2,838) | 690 (190–961) | 0.001[b] |
| Cumulative benzodiazepine dose[a], median (IQR), mg | 148 (110–688) | 789 (536–1,601) | 334 (195–401) | 0.004 |
| Number of attempts of opioid weaning, median (IQR) | 1 (1) | 1.5 (1–2) | 1 (1) | 0.08 |
| Number of attempts of benzodiazepine weaning, median (IQR) | 1 (1–5) | 2 (1–3) | 2 (1–2) | 0.14 |

IQR = interquartile range, MV = mechanical ventilation, WS = withdrawal syndrome.

[a]Reflect the last cumulative doses presented at the time of probable or questionable WS or the last cumulative dose at the last bedside measurement for those who never developed WS.

[b]The differences were significant after adjusting alpha ($\alpha$) for 13 comparisons ($p < 0.004$).

Fisher exact test was used for categorical variables and Kruskal–Wallis test was used for continuous variables.

### Potential Predictors of Development of Probable WS

As shown in **Table 2**, we evaluated several candidate models for WS (probable vs no), in terms of their fit, using AIC and BIC. When comparing the first five models, multivariate model no. 4, with age, benzodiazepine and opioid cumulative dose, days on benzodiazepine and opioid, previous drug use, and duration on MV presented the best AIC and BIC. After adjusting for all of these variables in the model, we found the following: (1) increase in age was inversely associated with the odds of developing probable WS (odds ratio [OR] = 0.96; 95% CI, 0.93–0.99), (2) there was a 10% increase in the odds of probable WS (OR = 1.10; 95% CI, 1.04–1.17) for each 100 mg increase in the cumulative dose amounts of opioids prior to weaning, (3) those with previous drug use compared with drug naive patients had 5.21 (95% CI, 2.11–12.84) times higher odds of having probable WS (**Table 3**, Model No. 4).

We then analyzed the addition of the RASS and delirium to the regression model no. 6 and found that doing so improved the model fit significantly, as reflected by AIC, BIC, and the pseudo-$R^2$ statistics (Table 2). In this model (Table 3, Model No. 6), after adjusting for all variables, the older age no longer had the protective effect. On the other hand, the association between WS and duration on MV, as well as number of days on opioids strengthened and became significant. After additionally adjusting for delirium and RASS, each additional day on MV was associated with an 8% increase in odds of probable WS (OR = 1.08; 95% CI, 1.02–1.15). In this model, interestingly, the number of days on opioids prior to weaning process was protective for the odds of developing probable WS (OR = 0.70; 95% CI, 0.50–0.97). In addition, the odds of presence of probable WS were 4.13 (95% CI, 2.09–8.16) for every one-point increase in RASS score, and patients with delirium had 2.69 times higher odds of probable WS compared with those without delirium (95% CI, 1.01–7.14) (Table 3, Model No. 6).

**TABLE 2. Model Fit Statistics for Different Candidate Models**

| Models | Log Likelihood | degree of freedom | Akaike Information Criterion | Bayesian Information Criterion | R2 |
|---|---|---|---|---|---|
| No. 1<br>Age, APACHE score, benzodiazepine and opioid cumulative dose, days on benzodiazepine and opioid, previous drug user, duration on MV, LOS-ICU, LOS-hospital | −78.1 | 11 | 178.2 | 213.5 | 0.17 |
| No. 2<br>Age, APACHE score, benzodiazepine and opioid cumulative dose, days on benzodiazepine and opioid, previous drug user, duration on MV, LOS-ICU | −78.3 | 10 | 176.6 | 208.7 | 0.17 |
| No. 3<br>Age, benzodiazepine and opioid cumulative dose, days on benzodiazepine and opioid, previous drug user, duration on MV, LOS-ICU | −78.4 | 9 | 174.7 | 203.7 | 0.17 |
| No. 4<br>Age, benzodiazepine and opioid cumulative dose, days on benzodiazepine and opioid, previous drug user, duration on MV | −78.8 | 8 | 173.6 | 199.4 | 0.17 |
| No. 5<br>Benzodiazepine and opioid cumulative dose, days on benzodiazepine and opioid, previous drug user, duration on MV | −81.5 | 8 | 179.0 | 204.7 | .14 |
| No. 6<br>Age, benzodiazepine and opioid cumulative dose, days on benzodiazepine and opioid, previous drug user, duration on MV, Richmond Agitation Sedation Scale and delirium | −52.5 | 10 | 125.0 | 154.9 | 0.44 |

APACHE= Acute Physiology and Chronic Health Evaluation II, LOS= length of stay, MV= mechanical ventilation, RASS=.
Lower values of both Akaike information criterion and Bayesian information criterion indicate better model fit.

## DISCUSSION

Opioid and benzodiazepine WS in adult ICU patients have been given little attention in the past years. Literature has established that there is a lack of recognition of WS due to the similarity between WS and delirium, the worsening of the critical illness, and the use of multiple drugs that have the potential to cause withdrawal if they are discontinued together (28, 29).

One third of our sample (17/50) had a history of illicit drug use prior to their admission to ICU. In light of an increased number of ICU admissions for opioid overdose care (30), it is important to include those with a pre-existing drug condition in ICU studies of WS. When evaluating just our drug naive patients from the total sample, 38% developed probable WS, which is similar to the occurrence reported in the study by Korak et al (11). Although Wang et al (10) studied trauma patients, as did we, they found a relatively lower occurrence of WS in their drug naive patients (17%) compared with our drug naive patients (38%); however, they attributed the low occurrence in their drug naive patients to the short duration of both MV and opioid exposure and their short-term evaluation of WS. It is important to point out that each one of those studies used a different instrument to measure WS, possibly influencing the findings of the study. In addition, in order to evaluate each study findings, it is important to take into account other differences between studies such as patient diagnosis, inclusion/exclusion criteria (e.g. prior drug users, alcohol use history), and timing of data collection (i.e. retrospective vs prospective).

WS literature in adults has generally not reported the specific sign and symptoms that commonly occur. However, in the abstract of one recent study of opioid-associated WS that enrolled 25 ICU patients, investigators reported similar signs and symptoms of WS found in our study (31). They included restlessness, high blood pressure, lacrimation, diarrhea, agitation, and hallucinations. Those investigators used a standardized form with potential WS sign and symptoms, and concomitantly, a physician assessed the patients with the DSM-5 criteria (31). Based on the findings of the mentioned study and ours, the research basis for identifying WS may be evolving.

In our study, younger participants had higher odds of WS (Table 3, Model No. 4). Cammarano et al (7) also found a significantly higher occurrence of WS in younger versus older patients (mean age of 34.9 ± 4.6 vs 50.9 yr ± 4.0; $p = 0.017$). As expected, our patients who previously used drugs were significantly more likely to develop probable WS than drug naive patients. Cammarano et al (7) did not find differences; however, they only had two patients with a history of drug use. Similar to our findings, Cammarano et al (7) found that patients in the WS group had longer durations of MV than did non-WS patients ($p = 0.049$). Furthermore, like us, Wang et al (10) found that patients in the WS group had a longer duration of MV, longer ICU stays, and higher cumulative opioid dose prior the weaning, but their findings were not statistically significant.

In our multivariate analysis that included RASS and CAM-ICU findings, age did not continue to be a predictor of WS (Table 3, Model No. 6). However, the RASS and delirium findings, when added to the model, significantly increased the model fit. That is, we found that they are both related to WS. From a conceptual and clinical perspective, it could be important for providers to recognized agitation/restlessness and delirium when caring for ICU patients being weaned from opioids and/or benzodiazepines.

**TABLE 3. Adjusted Odds Ratios and 95% CIs for the Development of Probable Withdrawal Syndrome, According to Potential Predictors**

| Variable | Adjusted OR[a] (95% CI) | SE | z | *p* |
|---|---|---|---|---|
| Model No. 4 | | | | |
| Age | 0.96 (0.93–0.99) | 0.02 | −2.30 | 0.022 |
| Benzodiazepine cumulative dose[b,c] | 0.95 (0.90–1.01) | 0.03 | −1.55 | 0.121 |
| Opioid cumulative dose[b,c] | 1.10 (1.04–1.17) | 0.03 | 3.11 | 0.002 |
| Days on benzodiazepine[b] | 1.18 (0.89–1.56) | 0.17 | 1.13 | 0.259 |
| Days on opioid[b] | 0.83 (0.65–1.07) | 0.10 | −1.46 | 0.145 |
| Previous drug use | 5.21 (2.11–12.84) | 2.40 | 3.59 | <0.0005 |
| Duration on MV | 1.01 (0.97–1.06) | 0.02 | 0.46 | 0.648 |
| Model No. 6 | | | | |
| Age | 0.98 (0.93–.1.02) | 0.02 | −0.98 | 0.329 |
| Benzodiazepine cumulative dose[b,c] | 0.94 (0.87–1.01) | 0.04 | −1.66 | 0.097 |
| Opioid cumulative dose[b,c] | 1.14 (1.05–1.23) | 0.05 | 3.23 | 0.001 |
| Days on benzodiazepine[b] | 1.28 (0.90–1.84) | 0.24 | 1.38 | 0.168 |
| Days on opioid[b] | 0.70 (0.50–0.97) | 0.12 | −2.16 | 0.031 |
| Previous drug use | 5.65 (1.82–17.51) | 3.26 | 3.00 | 0.003 |
| Duration on MV | 1.08 (1.02–1.15) | 0.03 | 2.53 | 0.011 |
| Richmond Agitation Sedation Scale score | 4.13 (2.09–8.16) | 1.44 | 4.07 | <0.0005 |
| Delirium | 2.69 (1.01–7.14) | 1.34 | 1.98 | 0.047 |

MV= mechanical ventilation, OR = odds ratio.

[a]All variables assessed in this table were included in the mixed-effects logistic regression models.

[b]Prior to weaning process.

[c]For each 100 mg increase.

The final model (Table 3, Model No. 6) also showed that cumulative opioid dose amounts prior to weaning were associated with development of WS, although the number of days that patients received opioids was protective. In our study, as expected, days on opioids and cumulative opioid dose were strongly correlated (Spearman correlation coefficient = 0.78, not shown in the tables). The nature and the strength of the relationship between these two variables could be the reason behind our findings: in the multivariate regression analysis, while holding the cumulative opioid dose constant, the "days on opioid" variable showed a slightly protective odds ratio for WS (OR = 0.70; 95% CI, 0.50–0.97). That is, given the same cumulative dose of opioid, patients with longer duration on opioid (and therefore, lower daily dose) had lower odds of developing WS. Another explanation for this finding is that there are several factors that can cause differences in opioid tolerance, the precursor to WS, at the opioid receptor level (32). Cumulative doses may affect the opioid receptor differently than length of time receiving opioids. In addition, genetic differences in opioid receptor synthesis and variable opioid receptor affinity, the difference in type of opioid administered, and the use of continuous versus intermittent administration may be influential factors (32). Use of multimodal analgesia may help to counteract development of WS through reduction of opioid amounts administered to the patient (32). However, further research is warranted on time versus amount differences in opioids and their risk for WS.

This study has several strengths. The assessment of WS was done using a prospective approach two times a day for 72 hours or more. Furthermore, in the absence of an instrument validated to measure opioid and benzodiazepine WS in ICU adults, we developed a checklist using several reliable sources: the DSM-5 criteria, *International Classification of Diseases,* 10th Edition criteria WS, and symptoms identified in previous adult WS studies. Therefore, the checklist had content validity. Furthermore, given that our study was exploratory in nature, we were able to conduct several analyses by constructing various models between patient- and clinical-related factors and the probable presence of WS.

Our study has notable limitations. Consistent with other WS studies in ICU (7, 8, 11, 31, 33), our sample was small. In addition, the TICU did not have a protocol for daily sedation interruption or a pain management protocol. Therefore, there was a large degree of variability in the opioid and/or benzodiazepine weaning process between patients; this could have influenced differences in WS development. In addition, we were unable to evaluate some symptoms on the checklist in patients with RASS –3 to –5 such as hallucinations, delusions, illusions, dysphoria, nausea, insomnia, and delirium. Also, the intensity of the probable WS sign and symptoms

was not evaluated. Our checklist has not yet undergone a formal validation process and reliability testing. Interrater or intrarater reliability was not possible because only one person performed all measures and the occurrence of WS was not constant between measurements. Finally, the signs and symptoms on our checklist are not specific for WS; thus, we could not rule out other conditions associated with these signs or symptoms. Further research on the psychometric characteristics of our checklist is warranted.

## CONCLUSIONS

In our study, we identified probable WS in a sample of TICU patients through observation of several associated signs and symptoms. We identified certain factors that were associated with WS such as increased agitation, previous drug user, and greater cumulative doses of opioids prior to the weaning process. We also found that patients who developed probable WS spent more time on MV and had increased lengths of time in both ICU and hospital. They also had associated agitation/restlessness and delirium as assessed by valid, reliable, feasible tools frequently used in the ICU, the RASS and the CAM-ICU. Further research should focus on the validation of the opioid and benzodiazepine WS checklist in larger samples of ICU patients at risk for WS. Prospective studies are warranted on methods to promote analgesia and sedation while preventing WS. Finally, exploring the occurrence of WS after patient discharge may emphasize the importance of identifying and treating WS in ICU patients.

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