Pain, Anxiety, and the Continuous Use of Opioids and Benzodiazepines in Trauma Intensive Care Unit Survivors: An Exploratory Study

Carmen Mabel Arroyo-Novoa, PhD, RN, FCCM*; Milagros I. Figueroa-Ramos, PhD, RN, FCCM*; Kathleen A. Puntillo, PhD, RN, FAAN, FCCM†

Objective: To evaluate at-home opioid and benzodiazepine use, the degrees of pain and anxiety, and the incidence of probable withdrawal in post-discharge Trauma Intensive Care Unit (TICU) survivors.

Methods: This was an exploratory study of post-TICU survivors who had participated in a previous study of opioid and benzodiazepine withdrawal. We surveyed survivors by telephone asking for retrospective information (during their first 4-months post-discharge- *Time 1*) and current information (around 2-years post-discharge- *Time 2*).

Results: A mostly male (82%), young (median 38 years [IQR, 28–52]) sample of 27 TICU survivors reported using opioids (56%) at *Time 1* for a median of 30 (IQR,14–90) days. Twelve percent of 26 survivors were still using opioids at *Time 2*. Sixty percent of the survivors had pain during *Time 1*, a median pain score of 6 (IQR, 5–8) on a 0-10 numeric rating scale (NRS).; 57% had pain at *Time 2*, median NRS score=6 (IQR, 4–7). Sixty-five percent of survivors had anxiety during *Time 1*, NRS median=7 (IQR, 5–9); 50% had anxiety at *Time 2*, NRS median= 6 (IQR, 3–7). At Time 1, 26% used prescribed benzodiazepines, and 12% used benzodiazepines at Time 2. Five and one of the 27 patients reported symptoms of opioid or benzodiazepine withdrawal, respectively, upon discontinuation or weaning.

Conclusion: Many TICU survivors had discontinued opioid/benzodiazepine prescriptions by 4-months post-discharge while half reporting pain/anxiety for up to 2-years. Investigating the effects of acute-to-chronic pain in ICU survivors and gaining a better understanding of the mechanisms of prolonged opioid use are warranted.
[*P R Health Sci J 2022;41(3):111-116*]

Key words: Pain, Opioids, Anxiety, Benzodiazepines

Many intensive care unit (ICU) patients are treated with opioids, benzodiazepines, or both. The use of high and prolonged doses of these drugs in trauma ICUs (TICUs) may be unavoidable due to the patients' clinical conditions. Their prolonged use is sometimes associated with the development of drug tolerance and physical dependence (1–3). Drug tolerance, here meaning opioid or benzodiazepine tolerance, is the need to increase a medication dose to obtain the same effect received from a smaller dose (4). Physical dependence is the development of unpleasant physical symptoms, manifesting as withdrawal syndrome, brought on by drug cessation (4, 5). The sequelae from the prolonged TICU use of opioids and benzodiazepines after TICU patients are discharged are unknown.

We do know that some ICU survivors are discharged from the hospital with prescriptions for opioids (for pain management) and/or benzodiazepines (for anxiety, posttraumatic stress disorder, or both) (6, 7). Scales and colleagues (7) collected hospitals-databases from discharged patients 65 years and older, finding that ICU patients were more likely to be prescribed benzodiazepines than were non-ICU patients. Other studies have investigated opioid prescriptions beyond hospital discharge for both ICU and non-ICU trauma patients. For example, 54% of patients from multiple trauma centers received opioid prescriptions at discharge (8). A chart review of 235 level I trauma center patients identified that a significant predictor of a discharged patient's receiving an opioid prescription was ICU admission as an orthopedic trauma patient (9). At another level I trauma center, 79% of 101 patients developed chronic pain four months after discharge (n = 80), and 26% were still using opioids (10). Neither the patient's pain at discharge nor the rationale for opioids prescriptions were described in any of these studies.

*Professor, School of Nursing, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico; †Professor Emeritus, School of Nursing, University of California, San Francisco, California, USA

The authors have no conflicts of interest to disclose.

Address correspondence to: Carmen Mabel Arroyo-Novoa, PhD, RN, FCCM, Professor, University of Puerto Rico Medical Sciences Campus, School of Nursing, PO Box 365067, San Juan, PR 00936-5067. Email: carmen.arroyo1@upr.edu

We previously conducted a study of TICU patients who had received at least five days of opioids and/or benzodiazepines (11). We found that 44% of 50 patients developed a probable withdrawal syndrome during their TICU stay. Of the 50 patients studied, 69% and 31%, respectively, received an opioid or a benzodiazepine prescription at hospital discharge (12, 13). Continuous use of opioids and benzodiazepines by discharged TICU survivors and indications and possible implications of such use are not yet well studied. Thus, this exploratory study's primary purpose was to investigate the use of opioids and benzodiazepines and consequences of that use in a previously studied sample of TICU survivors following hospital discharge. We also explored the survivors' post-discharge pain and anxiety.

Methods

Design

We conducted an exploratory, cross-sectional follow-up study of discharged TICU survivors using a telephone survey. The institutional review board (IRB) of the University of Puerto Rico, Medical Sciences Campus, approved this study (#A5570218).

Measures

A survey was developed specifically for this follow-up study. During a single call, respondents were asked to answer questions about two time periods: *Time 1* was the time between their hospital discharge and four months after discharge; *Time 2* was the current time (i.e., the time of the survey, approximately two years post-discharge). The survey included questions related to the use of opioids, benzodiazepines, and other medications to treat pain and/or anxiety; pain presence and intensity; anxiety presence and intensity; and signs and symptoms related to opioid and/or benzodiazepine tolerance, dependence, and/or having probable withdrawal syndrome. To assess the survivors' reports of having *probable* opioid or benzodiazepine withdrawal syndrome at the two assessment times, a checklist was used that included the withdrawal signs and symptoms of opioids and benzodiazepines according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (5) and the *International Classification of Diseases* (ICD-10) (14). Taking both DSM-5 and ICD-10 withdrawal criteria into account and given that the checklist has not undergone a formal validation process we named the syndrome as "*probable*" withdrawal. This was defined as presence of 3 or more signs or symptoms associated with opioid withdrawal or 2 or more signs or symptoms associated with benzodiazepine withdrawal (Table 1) (5). Survivors were asked to remember whether they had developed any of those signs or symptoms when they decreased or discontinued their medications. Finally, we asked the survivors whether they perceived that they had developed a dependence problem due to medications used.

Table 1. Probable Opioid and Benzodiazepine withdrawal criteria

Opioid signs and symptoms	Benzodiazepine signs and symptoms
□ nausea or vomiting	□ nausea or vomiting
□ anxiety or restlessness	□ anxiety or agitation
□ muscle aches	□ increase in pulse
□ increased tearing	□ increase in blood pressure
□ runny nose or sneezing	□ hallucinations or illusions (see, listen, or feel strange things)
□ bristling/goosebumps	□ convulsions
□ increased sweating	□ increased sweating
□ diarrhea	□ headache
□ fever	□ general weakness
□ insomnia/ cannot sleep	□ shaking hands, tongue, or eyelids
□ abdominal cramps	□ insomnia/ cannot sleep
□ yawning	

To assess pain and anxiety intensity, we used two 0 to 10 numeric rating scales (NRS), in which 0 was equal to no pain/anxiety and 10 was equal to the worst pain/anxiety imaginable. In a recent review, (15) the NRS was evaluated as the optimal scale for acute pain assessment in adults, with slightly better psychometric properties than other scales for pain measurements. The NRS has also been used in multiple clinical settings for anxiety measurements (16–18). For this study, mild pain corresponded to an NRS score of 1 to 3, moderate pain corresponded to an NRS score of 4 to 5, and severe pain corresponded to an NRS score of 6 to 10 (19). The data collection form also had open-ended, clarifying questions.

Participants

In the original study (11), we recruited 50 adult TICU patients exposed to opioids or benzodiazepine for 5 days or more at the Puerto Rico Trauma Hospital. In this follow-up study, TICU survivors from the original study were included if they were living in their own house or living with a family member or significant other, whether they had exhibited a probable withdrawal syndrome in the TICU or not. They were excluded if they were institutionalized in a long-term care. In some cases, family members and/or significant others were asked to participate as informants or to help survivors answering questions. They were included if they were 21 years or older and lived with the survivor since they were discharge from the hospital. Authorization to obtain patient contact information from the patients' records was obtained from the IRB and the administration of the Puerto Rico Trauma Hospital.

Procedures

Survivors were contacted by telephone 25 (24–26) months after hospital discharge. After obtaining verbal consent from the patient and a survivor/family member/significant other, the surveys, approximately 15 to 30 minutes in length, were conducted in Spanish. The same person (CMA-N) conducted all survey interviews, which standardized the survey procedure. An ad hoc plan to manage a patient's potential distress during the

survey was developed and approved by the IRB. However, we did not to have to apply the plan during any survey.

Statistical analysis

Descriptive statistics were calculated for continuous variables and frequencies, for categorical variables. Mann-Whitney U test was performed to compare opioids doses received in the previous study in patients who developed versus did not develop probable withdrawal syndrome in the current study. Data are described using medians (IQR) and frequencies (%).

Results

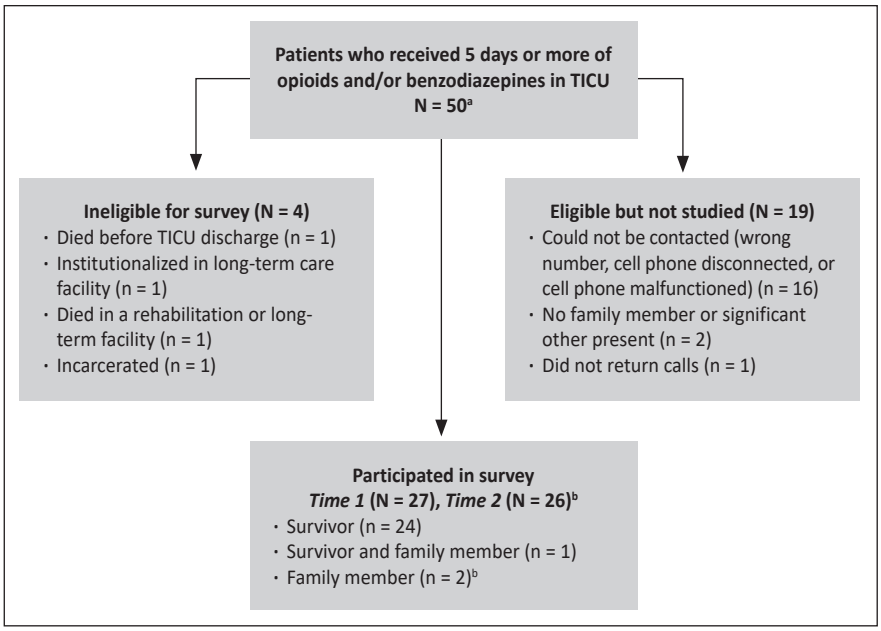

Figure 1. Study Flow Chart. TICU= Trauma Intensive Care Unit. [a]Arroyo CM et al. Crit Care Explorations, 2:e0089, 2020. [b]Information from 1 survivor for *Time 2* not available (patient died 1 year after TICU discharge).

We interviewed 27 survivors about *Time 1* experiences and 26 survivors about their current (*Time 2*) experiences. On three occasions, we spoke to a survivor's spouse/sibling, who helped with the survey or served as a surrogate (see Figure 1). The majority (82%) of the survivors were male with a median age of 38 (28–52.3). In the original study, most of these survivors (67%) were admitted to the TICU for blunt trauma and 33% for penetrating injury, and stayed in the TICU for 9 (6-17) days and in the hospital for 19 (13- 29) days. Of the 27 survivors, one used oxycodone for recreation, and two were prescribed benzodiazepines prior TICU admission. All 27 had received opioids when in the TICU, and 24 had received benzodiazepines (12).

Opioid use and pain

Sixteen survivors (59%) had received an opioid prescription at hospital discharge, but five had not used the prescribed drugs during *Time 1*. Four others who had not received an opioid prescription at discharge experienced pain and were prescribed an opioid after discharge. Thus, during the *Time 1* period, encompassing the four months post-discharge, 15 (56%) patients used prescribed opioids (Table 2). The opioid (tramadol) prescribed at discharge for one of the survivors did not relieve his pain, and he acquired a non-prescribed opioid (oxycodone with acetaminophen) on the "street" since it was the one that had been administered to him in the hospital. Once his pain was relieved, he discontinued the opioid. For the 13 survivors who discontinued opioid use in *Time 1*, their use lasted 30 (14–90) days. No survivor reported the need to increase their opioid dose during *Time 1*. Seventeen survivors used non-opioid agents, in combination with an opioid (n = 7) or alone (n = 10).

During *Time 1*, five survivors of the 15 (33%) who were using prescribed opioids reported developing 3 or more opioid withdrawal-related symptoms when discontinuing opioids. These five survivors had received a cumulative dose of 2,953 mg (2,427–5,936) of morphine-equivalent opioids for 21 days (16–35) from the first day receiving opioids until up to 3 days after opioid weaning. For comparison, the 10 who did not report withdrawal-related symptoms at home had received

Table 2. Opioid and other analgesics use

Analgesics	Time 1 *n (%)*	Time 2 *n (%)*
Use of prescription opioids	15 (56)*	3 (12)
Oxycodone/acetaminophen	9 (33)	1(4)
Tramadol/acetaminophen	7 (26)	0
Tramadol	5 (18)	2 (8)
Oxycodone	1 (4)	0
Use of non-prescription opioids	1 (4)	0
Oxycodone/acetaminophen	1 (4)	0
Use of non-opioids in combination with opioids or alone	17 (63)*	9 (33)*
Acetaminophen	9 (33)	4 (15)
Ibuprofen	9 (33)	5 (18)
Gabapentin	1 (4)	1 (4)
Acetaminophen/diphenhydramine	1 (4)	0
Nabumetone	1 (4)	0
Baclofen	1 (4)	0
Diclofenac	1 (4)	0
Medical cannabis	0	1 (4)

Time 1= during the first 4 months after hospital discharge (n= 27 patients); Time 2= time of the interview approximately 2 years after hospital discharge (n = 26 patients). *Some survivors used more than one medication.

Table 3. Benzodiazepine and Antidepressant use

Medications	Time 1 N (%)	Time 2 N (%)
Use of prescription benzodiazepine	7 (26)	2 (8)
Lorazepam	2 (7)	0
Clonazepam	5 (9)	2 (8)
Use of prescription antidepressant in combination with benzodiazepine	1 (4)	1 (4)
Trazodone	1 (4)	0
Mirtazapine	0	1 (4)

Time 1= during the first 4 months after hospital discharge (n= 27 patients); Time 2= time of the interview approximately 2 years after hospital discharge (n = 26 patients)

706 mg (171–1434) over 8 days (7–14) in TICU, a significant difference (p=.005) (12). Two of the five survivors who reported opioid withdrawal-related symptoms at home had also experienced probable withdrawal syndrome while in the TICU.

At *Time 2*, two survivors were still using prescribed opioids, and one additional survivor had received a new opioid prescription. Two were using tramadol and one was using oxycodone/acetaminophen (Table 2). One survivor who was still using a prescribed opioid for his pain reported that he believed he had developed an opioid dependency problem.

Twenty-five survivors (93%) recalled having pain during *Time 1*, with the median pain intensity score being 6 (5–8). Fifteen of these 25 survivors with pain (60%) had pain intensity scores of 6 or higher, indicating severe pain (19). Fourteen (54%) survivors reported still having chronic pain at *Time 2*, with their pain intensity score being 6 (4–7). Eight of these 14 survivors with pain (57%) had pain intensity scores of 6 or greater, reflecting severe pain (19). For those whose pain had stopped during *Time 1*, the time to no pain was 52.5 (30–120) days post-discharge.

Benzodiazepine use and anxiety

Six survivors (22%) received benzodiazepine prescriptions at hospital discharge. Two of the 6 survivors did not use benzodiazepines, and 1 did not know whether he had used a benzodiazepine during *Time 1*. Four others who had not received a prescription at discharge were prescribed a benzodiazepine, post-discharge, for anxiety. Thus, by *Time 1*, seven (26%) patients had been using prescribed benzodiazepines (Table 3). Benzodiazepine use continued for a median of 24 (14–30) days. At *Time 2*, the time of the interview, two of the seven patients were still using benzodiazepines (Table 3). Only one patient reported developing two or more benzodiazepine withdrawal symptoms when discontinuing benzodiazepine use during the first four months post-discharge.

Seventeen survivors (63%) recalled having anxiety during *Time 1*, with their median anxiety intensity score being 7 (5–9). Eleven of the 17 survivors with anxiety had anxiety intensity scores of 6 or greater. Twelve survivors (46%) reported still having anxiety at *Time 2*, with their median anxiety intensity score being 6 (3–7). Six of these 12 survivors with anxiety had anxiety intensity scores of 6 or more. For those whose anxiety had stopped before *Time 2*, the median time to no anxiety was 150 (83–210) days post-discharge.

Discussion

Our study is the first one known to survey discharged trauma survivors who experienced prolonged use and large amounts of benzodiazepines and/or opioids when in the TICU. While our sample size was small, we are able to provide new information based on survivors' self-reports of post-hospital drug use and withdrawal as well as of ongoing pain, and anxiety.

Over half of our sample survivors (59%) who had been discharged after a traumatic event, were prescribed opioids at discharge. This incidence is similar to that found in a sample of over 33,000 trauma survivors, 54.3% of whom were prescribed opioids (8). Yet, while one half of our sample reported using prescribed opioids, most had stopped by four months post-discharge, and one third were using non-opioid analgesics for pain. Simultaneously, more than half reported their pain to be severe (6 or above on the NRS scale). Adequate attention to pain management after a traumatic injury, beginning in the ICU and continuing for a period after discharge, might help avoid an acute-to-chronic pain transition (20).

Yet, nearly one-third of our survivors were still reporting severe chronic pain approximately two years post-discharge, and three were still using opioids. Recently, the International Association for the Study of Pain (IASP) developed a specific definition of chronic posttraumatic pain that has become part of IASP's nomenclature: pain that develops or increases in intensity after a tissue trauma (accidental) and persists beyond three months (21). Despite our patients having access to opioids post-discharge, with 63% of them using non-opioid analgesics along with opioids, the acute-to-chronic pain transition of these individuals was not well controlled. Trevino and colleagues (22) also found a high incidence of chronic pain in trauma patients, with 80 of 101 patients reporting pain at four months post-discharge. Jenewein and colleagues (23) found that 44% of the 90 ICU trauma patients suffered from chronic pain three years after their accident. In situations like these, chronic pain becomes the disease (20). It can be accompanied by posttraumatic stress disorder (24) and impaired quality of life (22). Indeed, many of our patients were experiencing anxiety. Eleven percent and 8% of the patients were using benzodiazepines at *Time 1* and *Time 2*, respectively, presumably for anxiety or sleep problems. Co-administration of benzodiazepines and opioids can cause increased morbidity linked to, among other issues, risks of overdose from respiratory depression and psychiatric states such as depression (25).

It is essential to acknowledge that long-term opioid use after hospitalization is a growing concern, particularly considering the opioid epidemic. In a recent study (26), 14,120 of 353,000 postsurgical veterans (almost 4.1%) had developed new persistent opioid use after an ICU stay. These investigators did

not determine why patients were still receiving opioids. Perhaps the patients were still having unresolved pain. However, those investigators did note a 39% decrease over three years in the odds of persistent post-discharge opioid use. Yaffe and colleagues (27) found that 12.2% of 2,595 elderly medical-surgical ICU patients used opioids post discharge, with the percentage decreasing to 4% at 48 months. Unlike our participants, the individuals in these two samples (26, 27) were not trauma patients and were older than our sample. Of almost 40,000 discharged elderly trauma patients, 38% filled an opioid prescription within three months of discharge, and 11% filled a prescription one year after their trauma (28). What these statistics are lacking are both the reason that the discharged patients were prescribed the opioids and the number of patients who continued to require these drugs for pain management. A more extensive longitudinal study is warranted to evaluate the appropriateness and effectiveness of prescribed opioids.

Our sample was unique in that, to our knowledge, no previous study has focused on predominantly younger ICU patients who received opioids over a prolonged period, with some of them having experienced opioid withdrawal in the ICU. Important questions remain: Why were some of our patients experiencing chronic, severe pain? Could those who reported experiencing severe pain for up to two years post-discharge have developed central sensitization? Central sensitization is a process whereby neurons in the central nervous system become hyperexcitable, and the threshold for nociceptive processing lowers over time (29). Furthermore, due to the large and prolonged opioid doses our patients received in the ICU and afterward, some of these patients could also have been experiencing a hyperalgesic response to the opioids. Opioid-induced hyperalgesia (OIH) is a state of enhanced pain sensitivity that is associated with an increase in opioid use, which results in an augmented perception of pain (30). Accordingly, then, does opioid use help or hinder chronic pain? Given the apparent lack of opioid effectiveness and the possibility of physiologic adverse effects (i.e., central sensitization and OIH) when these drugs are used, some survivors may have benefited from the use of neuropathic pain medications. Only one patient reported using gabapentin, a medication frequently used for neuropathic pain (31).

Five of our survivors had received high doses of opioids while in the TICU. These same five patients reported suffering from probable withdrawal from their opioids in the first four months after discharge. Questions to be considered in a larger sample of post-discharge patients include the following: (1) Do previous withdrawal episodes and/or having a previous history of receiving high doses of opioids lower the threshold for future withdrawal from dependency-inducing drugs such as opioids? (2) What surveillance measures and discharge instructions could prevent post-discharge opioid withdrawal? (3) What is the best tapering method to avoid withdrawal in a community sample of patients using oral opioids? Puntillo and Naidu (32) present a decision tree that highlights the interplay among pain assessment, pain management, opioid risk assessment, opioid benefit, and opioid management for community-based care. A more granular analysis of these issues in a larger sample is warranted.

Our study, while original, is limited by the small number of discharged trauma patients who were available for the follow-up survey; thus, a sampling bias might have existed. In addition, since patients did not answer questions until approximately two years after their hospital discharge, there may have been recall bias. The small sample size also did not permit use of inferential statistics to evaluate factors associated with the patients' continuous pain and opioid use. Finally, results from our study have limited generalizability because we recruited only trauma patients, ICU patients who had been discharged from only one trauma ICU, and our patient sample was relatively young. Nevertheless, we have obtained important data that generated intriguing questions for future research.

In conclusion, information obtained from post-discharge trauma patients who may have experienced opioid withdrawal while in the ICU is important. A high percentage of these survivors received prescriptions for and used opioids, but some reported having severe pain for as long as two years after discharge. Investigating the effects of acute-to-chronic pain in ICU survivors and gaining a better understanding of the mechanisms of prolonged opioid use are warranted.

Resumen

Objetivos: Evaluar el uso de opioides y benzodiacepinas, la intensidad de dolor y ansiedad y el síndrome de retirada post-alta en sobrevivientes de TICU. Métodos: Estudio exploratorio de sobrevivientes post-TICU que participaron en un estudio previo de síndrome de retirada de opioides y benzodiacepinas. Encuestamos por teléfono pidiendo información retrospectiva (durante los primeros 4-meses post-alta: *Tiempo-1*) e información actual (alrededor de 2-años post-alta: *Tiempo-2*). Resultados: Una muestra mayormente masculina (82%), joven (38 años [RIQ, 28-52]) de 27 sobrevivientes de TICU informó haber usado opioides (56%) en *Tiempo-1*, con una mediana de 30 (RIQ, 14-90) días. El 12% de 26 seguían usando opioides en *Tiempo-2*. El 60% tuvo dolor durante el *Tiempo-1*, mediana 6 (RIQ, 5–8); 57% continuó con dolor crónico en el *Tiempo-2*, mediana 6 (RIQ, 4–7). El 65% de los sobrevivientes tuvieron ansiedad durante el *Tiempo-1*, mediana 7 (RIQ, 5–9); el 50% con ansiedad en *Tiempo-2*, mediana de 6 (RIQ, 3–7). En *Tiempo-1*, el 26% de los supervivientes usaban benzodiacepinas prescritas y el 12% continuaban usándolas en *Tiempo-2*. Cinco y uno de 27 pacientes informaron haber experimentado síntomas de retirada de opioides y benzodiacepinas, respectivamente, tras descontinuarlos o destete. Conclusión: Muchos de nuestros sobrevivientes de TICU habían descontinuado las prescripciones de opioides/benzodiacepinas a los 4 meses posteriores al alta, mientras la mitad informó dolor y ansiedad hasta 2 años. Se justifica investigar los efectos del dolor agudo a crónico en los sobrevivientes de ICU y obtener una mejor comprensión de los mecanismos del uso prolongado de opioides.

Acknowledgment

This work was supported by the National Institute on Minority Health and Health Disparities, Hispanic Clinical and Translational Research Education and Career Development Program [grant R25MD007607]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Cammarano WB, Pittet J-FF, Weitz S, Schlobohm RM, Marks JD. Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care unit patients. Crit Care Med 1998;26(4):676–684. doi: 10.1097/00003246-199804000-00015.
2. Brown C, Albrecht R, Pettit H, McFadden T, Schermer C. Opioid and benzodiazepine withdrawal syndrome in adult burn patients. Am Surg 2000;66(4):367–370.
3. Korak-Leiter M, Likar R, Oher M, et al. Withdrawal following sufentanil/propofol and sufentanil/midazolam. Sedation in surgical ICU patients: correlation with central nervous parameters and endogenous opioids. Intensive Care Med 2005;31(3):380–387. doi: 10.1007/s00134-005-2579-3.
4. American Society of Addiction Medicine. The ASAM National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. [Internet]. 2015. Available from: https://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf. Accessed July 17, 2020.
5. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed. Washington, DC: American Psychiatric Publishing, 2013.
6. Morandi A, Vasilevskis E, Pandharipande PP, et al. Inappropriate medication prescriptions in elderly adults surviving an intensive care unit hospitalization. J Am Geriatr Soc 2013;61(7):1128–1134. doi: 10.1111/jgs.12329.
7. Scales DC, Fischer HD, Li P, et al. Unintentional continuation of medications intended for acute illness after hospital discharge: A population-based cohort study. J Gen Intern Med 2016;31(7):196–202. doi: 10.1111/jgs.12329.
8. Chaudhary MA, Schoenfeld AJ, Harlow AF, et al. Incidence and predictors of opioid prescription at discharge after traumatic injury. JAMA Surg 2017;152(10):930–936. doi: 10.1001/jamasurg.2017.1685.
9. Flanagan CD, Wysong EF, Ramey JS, Vallier HA. Understanding the opioid epidemic: Factors predictive of inpatient and postdischarge prescription opioid use after orthopaedic trauma. J Orthop Trauma 2018;32(10):e408–e414. doi: 10.1097/BOT.0000000000001256.
10. Trevino CM, De Roon-Cassini T, Brasel K. Does opiate use in traumatically injured individuals worsen pain and psychological outcomes? J Pain 2013;14(4):424–430. doi: 10.1016/j.jpain.2012.12.016.
11. Arroyo-Novoa CM, Figueroa-Ramos MI, Balas M, Rodríguez P, Puntillo KA. Opioid and Benzodiazepine Withdrawal Syndromes in Trauma ICU Patients: A Prospective Exploratory Study. Crit Care Explor 2020;2(4):e0089. doi: 10.1097/CCE.0000000000000089.
12. Arroyo-Novoa CM. [Unpublished raw data of cumulative dose of opioids that patients received in Trauma Intensive Care Unit]. 2017.
13. Arroyo-Novoa CM, Figueroa-Ramos MI, Puntillo KA: Opioid use decreases while pain continues in trauma ICU survivors. A follow-up study [Abstract 1798]. In: Critical Care Medicine. 2020;48(1):1798. doi: 10.1097/01.ccm.0000649488.25504.3d.
14. World Health Organization: The ICD-10 classification of mental and behavioural disorders. Clinical descriptions and diagnostic guidelines. Geneva,1992.
15. Safikhani S, Gries KS, Trudeau JJ, et al. Response scale selection in adult pain measures: results from a literature review. J Patient Rep Outcomes 2018; 2(1):40. doi: 10.1186/s41687-018-0053-6
16. Walawender I, Roczniak W, Nowak D, et al. Applicability of the Numeric Scale for Anxiety Evaluation in Patients Undergoing Dental Treatment. Dent Med Probl 2015;52(2):205–214.
17. Fosnocht DE, Swanson ER. Pain and anxiety in the emergency department. Ann Emerg Med 2004;44(4):S87. doi: 10.1016/j.annemergmed.2004.07.284.
18. Clarke H, Kirkham KR, Orser BA, et al. Gabapentin reduces preoperative anxiety and pain catastrophizing in highly anxious patients prior to major surgery: a blinded randomized placebo-controlled trial. Can J Anaesth 2013;60(5):432–443. 10.1007/s12630-013-9890-1.
19. Dihle A, Helseth S, Paul SM, Miaskowski C. The exploration of the establishment of cutpoints to categorize the severity of acute postoperative pain. Clin J Pain 2006;22(7):617–624. doi: 10.1097/01.ajp.0000210905.57546.c1.
20. Kyranou M, Puntillo K. The transition from acute to chronic pain: might intensive care unit patients be at risk? Ann Intensive Care 2012;2(1):36. doi: 10.1186/2110-5820-2-36
21. The International Association for the Study of Pain. Chronic pain has arrived in the ICD-11 [Internet]. 2019. Available from: https://www.iasppain.org/PublicationsNews/NewsDetail.aspx?ItemNumber=8340. Accessed July 17, 2020.
22. Trevino CM, Essig B, DeRoon-Cassini T, Brasel K. Chronic pain at 4 months in hospitalized trauma patients: Incidence and life interference. J Trauma Nurs 2012;19(3):154–159. doi: 10.1097/JTN.0b013e318261d304.
23. Jenewein J, Moergeli H, Wittmann L, et al. Development of chronic pain following severe accidental injury. Results of a 3-year follow-up study. J Psychosom Res 2009;66(2):119–126. doi: 10.1016/j.jpsychores.2008.07.011.
24. Andersen TE, Andersen L-AC, Andersen PG. Chronic pain patients with possible co-morbid post-traumatic stress disorder admitted to multidisciplinary pain rehabilitation—a 1-year cohort study. Eur J Psychotraumatosl 2014;5(1): 23235. doi : 10.3402/ejpt.v5.23235.
25. Jones JD, Mogali S, Comer SD. Polydrug abuse: A review of opioid and benzodiazepine combination use. Drug Alcohol Depend 2012;125(1-2):8–18. doi: 10.1016/j.drugalcdep.2012.07.004.
26. Karamchandani K, Pyati S, Bryan W, et al. New persistent opioid use after postoperative intensive care in US veterans. JAMA Surg 2019;154(8):778–780. doi: 10.1001/jamasurg.2019.0899.
27. Yaffe PB, Green RS, Butler MB, Witter T. Is admission to the intensive care unit associated with chronic opioid use? A 4-year follow-up of intensive care unit survivors. J Intensive Care Med 2017;32(7):429–435. doi: 10.1177/0885066615618189.
28. Daoust R, Paquet J, Moore L , et al. Incidence and risk factors of long-term opioid use in elderly trauma patients. Ann Surg 2018;268(6):985–991. doi: 10.1097/SLA.0000000000002461.
29. Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and Molecular Mechanisms of Pain [Internet]. Cell 2009;139(2):267–284. doi: 10.1016/j.cell.2009.09.028.
30. Yi P, Pryzbylkowski P. Opioid Induced Hyperalgesia. Pain Med (United States) 2015;16(supp.1):S32–S36. doi: 10.1111/pme.12914.
31. Harvin JA, Kao LS. Pain management in the surgical ICU patient. Curr Opin Crit Care. 2020;26(6):628–33.
32. Puntillo K, Naidu RK. Measurement of Chronic Pain and Opioid Use Evaluation in Community-Based Persons with Serious Illnesses. J Palliat Med 2018;21(S2):S43–S51. doi: 10.1089/jpm.2017.0457.