



# Risk Factors Associated With Opioid/Benzodiazepine Iatrogenic Withdrawal Syndrome in COVID-19 Acute Respiratory Distress Syndrome

Journal of Pharmacy Practice  
2022, Vol. 0(0) 1–8  
© The Author(s) 2022  
Article reuse guidelines:  
[sagepub.com/journals-permissions](https://sagepub.com/journals-permissions)  
DOI: 10.1177/08971900221116178  
[journals.sagepub.com/home/jpp](https://journals.sagepub.com/home/jpp)  
SAGE

Melissa Vu Maffei, BS<sup>1,2</sup> , Spencer Laehn, PharmD, BCCCP<sup>1</sup>,  
Monica Bianchini, PharmD, MPH<sup>1</sup>, and Andy Kim, PharmD, BCCCP<sup>1</sup> 

## Abstract

**Background:** Mechanically ventilated COVID-19 acute respiratory distress syndrome (ARDS) patients often receive deeper sedation and analgesia to maintain respiratory compliance and minimize staff exposure, which incurs greater risk of iatrogenic withdrawal syndrome (IWS) and has been associated with worse patient outcomes. **Objective:** To identify potential risk factors and differences in patient outcomes associated with the development of IWS in COVID-19 ARDS patients. **Methods:** Retrospective analysis of ventilated COVID-19 ARDS intensive care unit (ICU) patients who received continuous intravenous (IV) analgesia and sedation for  $\geq 5$  days from March 2020–May 2021. Patients were classified as IWS and non-IWS based on receipt of scheduled oral sedative/analgesic regimens after cessation of IV therapy. Risk factors were assessed in univariate analyses and multivariable modeling. **Results:** A total of 115 patients were included. The final multivariable model showed: (1) each additional day of IV opioid therapy was associated with an 8% increase in odds of IWS (95% CI, 1.02–1.14), (2) among sedatives, receipt of lorazepam was associated with 3 times higher odds of IWS (95% CI 1.12–8.15), and (3) each 1-point increase in Simplified Acute Physiology Score (SAPS) II was associated with a 4% reduction in odds of IWS (95% CI 0.93–0.999). **Conclusion:** Prolonged and high dose exposures to IV opioids and benzodiazepines should be limited when possible. Additional prospective studies are needed to identify modifiable risk factors to prevent IWS.

## Keywords

iatrogenic withdrawal, sedation, analgesia, COVID-19, ARDS

## Introduction

Among mechanically ventilated patients, those with COVID-19 acute respiratory distress syndrome (ARDS) often receive deeper and prolonged courses of sedation and analgesia than their non-COVID counterparts, which has been associated with higher risk of coma and mortality.<sup>1–5</sup> These increased exposures may also place patients at greater risk for development of iatrogenic withdrawal syndrome (IWS), as repeated and sustained administration of opioids and/or benzodiazepines (BZDs) can result in reduced sensitivity and increased tolerance.<sup>6–8</sup> Development of IWS in the critically ill has been associated with worse patient outcomes, such as longer intensive care unit (ICU) and hospital length of stay (LOS), longer duration of mechanical ventilation (MV), and increased risk of delirium.<sup>2,9,10</sup> Current practice guidelines on ICU analgesia and sedation recommend light sedation targets with a focus on pain-management, minimization of BZD use, and regular sedation assessments.<sup>11,12</sup> However, application of

these principles may be particularly difficult given the challenges of caring for COVID-19 ARDS patients, such as the need to minimize staff exposure, reduce patient discomfort, and maintain respiratory compliance during prolonged MV with or without prone positioning.

The current body of literature on IWS in the critically ill adult population is sparse in comparison to pediatric patients. The Withdrawal Assessment Tool-1 and Sophia Observation withdrawal Symptoms scoring tools are used to assess IWS in pediatric populations, but validated IWS assessment tools are

<sup>1</sup>Denver Health Medical Center, Denver, CO, USA

<sup>2</sup>University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, CO, USA

### Corresponding Author:

Andy Kim, Department of Pharmacy, Denver Health Medical Center, 790 Delaware Street MC 0056, Denver, CO 80204, USA.

Email: [andy.kim@dhha.org](mailto:andy.kim@dhha.org)

not available for the adult population.<sup>13,14</sup> The creation of such a tool in the adult ICU population is challenging given the complexity of the patients and difficulties distinguishing symptoms of IWS from other common ICU-related complications.

Studies have found the incidence of IWS in the ICU ranges from 17-100%, but the true incidence is unknown. The wide range in current literature may be in part reflective of the variation in study design, as each used different criteria for identifying IWS and varied in sample sizes, ICU setting, minimum intravenous (IV) analgesic and/or sedative inclusion exposures, and follow-up periods.<sup>9,10,15-18</sup> In example, authors reporting a 17% occurrence of IWS noted their shorter IV analgesia exposure and shorter follow-up period may have limited their ability to capture IWS.<sup>15</sup> Conversely, authors reporting a 100% IWS occurrence had a small cohort size of 11 patients within a burn ICU, a population known to have much higher analgesia requirements than other ICU patient populations.<sup>18</sup> Despite some variability, studies have identified increasing cumulative doses and durations of opioids and BZDs, increasing durations of MV, receipt of neuromuscular blocking agents (NMBA), prior substance abuse, rates of opioid and BZD weaning, and younger age as potential risk factors for IWS in critically ill adults.<sup>9,10,15-18</sup> While these studies were conducted in critically ill patients with a majority receiving MV during admission, to our knowledge, studies detailing risk factors for IWS within COVID-19 ARDS patients have yet to be conducted. Given the increased risk for IWS in these patients and negative outcomes associated with its development, identification of risk factors for IWS in COVID-19 patients may be useful to clinicians as the first step in prevention.

The objectives of this study are to (1) identify potential risk factors associated with the development of IWS in mechanically ventilated COVID-19 ARDS adult patients, and (2) assess the impact of IWS on patient outcomes, specifically hospital and ICU LOS, and duration of oral therapy in the IWS group.

## Methods

### Study Design

This is a retrospective cohort of adult patients hospitalized within Denver Health's Medical ICU from March 2020–May 2021. Denver Health Medical Center is a 525-bed safety net academic medical center and Level I trauma center. This study was reviewed and approved by the institution's Quality Improvement Review Committee.

### Participants

Patients 18 years of age and older were included in this study if they were admitted to the ICU, diagnosed with COVID-19 ARDS, received MV, and received continuous IV analgesia and sedation for  $\geq 5$  days. IWS was defined as the receipt of

scheduled oral opioid, benzodiazepine, and/or clonidine regimens after cessation of IV analgesics and sedatives while in the ICU. The initiation and choice of oral agent(s) was determined at the discretion of the treating team. Patients were excluded if they had received opioids, benzodiazepines, or clonidine preceding admission, based on their validated admission medication history. Patients who were initially admitted to the ICU for reasons unrelated to COVID-19 ARDS, such as trauma, were also excluded (Figure 1).

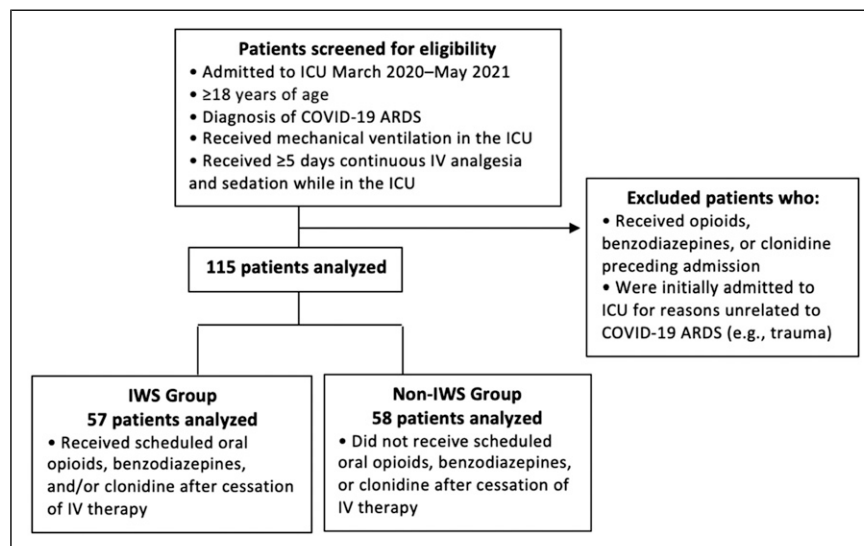
### Data Collection

Demographic and clinical data were extracted from the electronic health record (Epic, Verona, WI) and analyzed as potential risk factors, including: age, sex, body mass index (BMI), duration of MV, ICU and hospital LOS, Simplified Acute Physiology Score (SAPS) II, mean Richmond Agitation Sedation Scale (RASS) score on day 5 of ICU admission, admission survival, history of alcohol and/or substance abuse, renal dysfunction, receipt of neuromuscular blockade (NMB), mean PaO<sub>2</sub>/FiO<sub>2</sub> (P/F) ratios, and cumulative doses and durations of IV opioids, IV benzodiazepines, IV ketamine, dexmedetomidine, and propofol received in the ICU. The SAPS II score is a validated predictor of ICU mortality, with higher scores indicating increased mortality risk. The RASS score is a validated tool used to assess levels of sedation or agitation in adult ICU patients, with more negative scores indicating deeper levels of sedation and higher positive scores indicating increasing agitation. Cumulative doses and durations of scheduled oral opioids, benzodiazepines, and clonidine given in the ICU were also collected in the IWS group. Mean P/F ratios were collected on day 7 and day 14 of MV; respective values were not collected for patients who were mechanically ventilated <14 days.

All IV opioid and IV benzodiazepine doses were converted into IV morphine and IV lorazepam equivalents, respectively.<sup>19,20</sup> SAPS II scores were calculated manually for each patient using the poorest values within the first 24 hours of ICU admission.<sup>21</sup> Renal dysfunction was defined as the diagnosis of acute kidney injury at any point during admission, measured as an increase in serum creatinine by  $\geq 0.3$  mg/dL within 48 hours, an increase in serum creatinine to  $\geq 1.5$  times the baseline value within the past 7 days, or a urine output of <0.5 mL/kg/h over 6 hours. NMB was defined as receipt of continuous infusion of a NMBA at any point during ICU admission. Atracurium is the preferred NMBA at this institution in ICU patients requiring NMB.

### Statistical Analyses

Categorical variables were described using frequencies and compared using the  $\chi^2$  or Fisher's exact test, where appropriate. Continuous variables were described using means and compared using the Student's t-test or Wilcoxon-Mann-Whitney test, where appropriate. Risk factors were evaluated in univariate



**Figure 1.** Patient selection flow chart.

analyses, and those with a  $P$ -value of  $<.25$  were considered for multivariable analysis. Candidate models were constructed using forward stepwise selection and evaluated by fit in terms of lowest Akaike information criterion and Bayesian information criterion values. The results of univariate and multivariable analyses were reported as odds ratios (OR) and adjusted odds ratios, respectively, with corresponding 95% confidence intervals and  $P$ -values; a two-sided  $P$ -value of  $<.05$  was considered statistically significant. All statistical analyses were performed using JMP Pro 15.2.0 (SAS Institute Inc., Cary, NC).

## Results

### Patient Characteristics

Baseline characteristics of the 115 patients included in the analyses are shown in Table 1; 57 patients were categorized as “IWS” and 58 patients as “non-IWS.” The majority of patients were male (70%) with a mean age of 60 ( $\pm 14$ ) years, mean BMI of 32.6 ( $\pm 8.8$ ) kg/m<sup>2</sup>, and mean SAPS II score of 31.6 ( $\pm 12.1$ ). In total, 64.3% of patients survived admission, with numerically but not statistically lower survival in the non-IWS group. In patients on MV  $\geq 14$  days, the IWS group ( $n = 39$ ) had significantly higher P/F ratios on Day 14 compared to Day 7 (122 vs 136,  $P = .043$ ), whereas the non-IWS group ( $n = 22$ ) had significantly lower ratios on Day 14 (135 vs 117,  $P = .044$ ). All other baseline characteristics were similar between groups (Table 1).

Among IV analgesics, patients received fentanyl (98.3%), hydromorphone (35.7%), and/or morphine (13%). Among IV BZDs, patients received midazolam (88.7%) and/or lorazepam (31.3%). Among other IV sedatives, patients received propofol (95.7%), dexmedetomidine (76.5%), and/or ketamine (18.3%). More patients in the IWS group versus non-IWS group received a total of three or more IV sedatives (86% vs 60%) and a total of two or more IV analgesics (54% vs 33%)

(Supplemental Figures 1(a)-1(b)). There were no significant differences in average daily doses of morphine equivalents and individual IV sedatives (counting only patients who received the respective sedative). However, the IWS group received significantly longer durations of morphine equivalents and IV sedatives, apart from ketamine (Supplemental Figures 2(a)-2(e) and 3(a)-3(e)).

### Differences in Patient Outcomes in Iatrogenic Withdrawal Syndrome

Patients in the IWS group had significantly longer durations of both ICU and hospital LOS. After cessation of IV therapy, 98.2% of patients in the IWS group received oral opioids for an average of 15 days, 31.6% received oral BZDs for an average of 8.8 days, and 19.3% received oral clonidine for an average of 10.4 days, for a combined average of 11.4 days of oral therapy (Table 2).

### Potential Risk Factors in the Development of Iatrogenic Withdrawal Syndrome

Among variables analyzed, univariate analysis showed statistically significant associations between IWS and durations of IV opioid, BZD, dexmedetomidine, and propofol, as well as cumulative IV BZD, dexmedetomidine, and propofol dose. Each additional day of IV opioid, dexmedetomidine, and propofol was associated with an 11% increase in odds of IWS (95% CI, 1.06-1.17, 1.04-1.19, and 1.04-1.18, respectively), while each additional day of IV BZD was associated with a 10% increase in odds of IWS (95% CI, 1.04-1.16). Each 100 mg increase in cumulative IV BZD dose was associated with a 6% increase in odds of IWS (95% CI, 1.01-1.12). Additional significant associations in univariate analyses were receipt of lorazepam or hydromorphone, ICU LOS, and

**Table 1.** Baseline Characteristics and Clinical Variables.

Baseline Characteristics and Clinical Variables	Total	IWS (n = 57)	Non-IWS (n = 58)	P-value
Age, mean (SD)	60 (14)	61 (14.5)	59 (13.0)	.35
Male, n (%)	81 (70.4)	40 (70.2)	41 (70.7)	.95
BMI, mean (SD)	32.6 (8.8)	32.6 (8.6)	32.6 (9.1)	.99
SAPS II, mean (SD)	31.6 (12.1)	30 (11.9)	33 (12.2)	.18
History of EtOH abuse, n (%)	10 (8.7)	5 (8.8)	5 (8.6)	.98
History of substance abuse, n (%)	17 (14.8)	10 (17.5)	7 (12.1)	.41
NMB use, n (%)	103 (89.6)	52 (91.2)	51 (87.9)	.56
Renal dysfunction, n (%)	72 (62.6)	37 (64.9)	35 (60.3)	.61
Survived admission, n (%)	74 (64.3)	41 (71.9)	33 (56.9)	.09
Hospital length of stay, d, mean (SD)	33.9 (27.1)	45.9 (33.1)	22 (10.2)	<.0001
ICU length of stay, d, mean (SD)	18.2 (13.0)	23.4 (15.7)	13.1 (6.5)	<.0001
Duration of MV, d, mean (SD)	20.3 (16.9)	27.6 (20.0)	13.2 (8.6)	<.0001
RASS mean on day 5, mean (SD)	-2.47 (1.69)	-2.56 (1.67)	-2.38 (1.71)	.59
Mean P/F ratios in those MV ≥14 days				
Day 7, mean (SD)	127 (37)	122 (33)	135 (43)	.19
Day 14, mean (SD)	129 (43)	136 (40)	117 (47)	.09
Paired t-test p-value (day 7 vs day 14)		0.043	0.044	
Opioid type received				
Fentanyl, n (%)	113 (98.3)	56 (98.2)	57 (98.3)	1.00
Hydromorphone, n (%)	41 (35.7)	27 (47.4)	14 (24.1)	.009
Morphine, n (%)	15 (13.0)	8 (14.0)	7 (12.1)	.75
Sedative type received				
Midazolam, n (%)	102 (88.7)	50 (87.7)	52 (89.7)	.74
Lorazepam, n (%)	36 (31.3)	24 (42.1)	12 (20.7)	.013
Propofol, n (%)	110 (95.7)	57 (100)	53 (91.4)	.057
Dexmedetomidine, n (%)	88 (76.5)	46 (80.7)	42 (72.4)	.29
Ketamine, n (%)	21 (18.3)	14 (24.6)	7 (12.1)	.083
Cumulative IV opioid dose <sup>a</sup> , mg, mean (SD)	3811 (5542)	4817 (6502)	2822 (4229)	.016
Cumulative IV benzodiazepine dose <sup>b</sup> , mg, mean (SD)	630 (911)	827 (1139)	437 (555)	.023
Cumulative dexmedetomidine dose, mcg, mean (SD)	7550 (11 294)	11 063 (13 972)	4097 (6231)	.003
Cumulative propofol dose, mg, mean (SD)	31 762 (29 387)	40 074 (32 419)	23 593 (23 615)	.001
Cumulative ketamine dose, mg, mean (SD)	3620 (14 433)	4202 (10 859)	3048 (17 324)	.67
Cumulative duration IV opioid, d, mean (SD)	17.1 (12.3)	22.5 (13.5)	11.7 (8.2)	<.0001
Cumulative duration IV benzodiazepine, d, mean (SD)	9.8 (9.4)	12.7 (11.2)	6.9 (5.9)	.001
Cumulative duration dexmedetomidine, d, mean (SD)	6.6 (8.8)	9.4 (10.7)	3.8 (5.0)	.002
Cumulative duration propofol, d, mean (SD)	9.0 (7.3)	11.4 (8.1)	6.7 (5.7)	.0009
Cumulative duration ketamine, d, mean (SD)	1.0 (3.0)	1.4 (3.4)	0.6 (2.4)	.13

Abbreviations: BMI, body mass index; EtOH, alcohol; IWS, iatrogenic withdrawal syndrome; MV, mechanical ventilation; NMB, neuromuscular blockade; P/F, PaO<sub>2</sub>/FiO<sub>2</sub>; RASS, Richmond Agitation Sedation Scale; SAPS II, Simplified Acute Physiology Score II

<sup>a</sup>IV morphine equivalents.

<sup>b</sup>IV lorazepam equivalents.

**Table 2.** Percentages and Mean Durations of Oral Medications Received in the IWS (n = 57) Group After Cessation of IV Therapy.

Oral Medication	% (n) of Subjects Receiving	Mean Duration (days)
Opioid	98.2 (56)	15
Benzodiazepine	31.6 (18)	8.8
Clonidine	19.3 (11)	10.4
Total	—	11.4

duration of MV; each additional day of ICU LOS and MV was associated with a 9% increase in odds of IWS (95% CI, 1.04-1.14 and 1.04-1.13, respectively) (Table 3).

Variables considered for entry into the multivariable model were cumulative durations of IV opioid, benzodiazepine, dexmedetomidine, propofol, and ketamine, duration MV, ICU LOS, SAPS II score, and receipt of hydromorphone, lorazepam, and ketamine. Cumulative doses of all medications were not considered in the final multivariable model as they were deemed to be a redundant measure of cumulative durations. The final model included cumulative duration of IV opioid, ICU LOS, receipt of lorazepam, and SAPS II score. The final model resulted in the following: (1) each additional day of IV opioid therapy was associated with an 8% increase in odds of IWS (95% CI, 1.02-1.14), (2) receipt of lorazepam was associated with 3 times higher odds of IWS (95% CI 1.12-8.15), and (3) each 1-point increase in SAPS II score was associated with a 4% reduction in odds of IWS (95% CI 0.93-0.999).

## Discussion

Our study found longer durations of IV opioid and receipt of lorazepam were associated with increased odds of IWS, while increasing SAPS II score was protective against IWS. Despite current recommendations, deviations in sedation practices in

COVID-19 patients across many ICUs have been reported.<sup>1-5</sup> While sedative/analgesic overuse in COVID-19 ARDS patients and its potential for development of IWS have been well-described by previous authors,<sup>7,8</sup> this is the first study to assess potential risk factors associated with iatrogenic opioid/benzodiazepine withdrawal in COVID-19 patients to our knowledge.

### Duration of IV Sedative, Analgesic, and Mechanical Ventilation

Associations between durations of analgesia/sedation and IWS across existing literature are mixed. Similar to our findings, prior retrospective studies in critically ill, mechanically ventilated patients have found associations with both increased doses and durations of both IV opioid and sedative agents in IWS groups. These studies were conducted in surgical and/or trauma ICUs, and consisted of comparatively smaller cohorts (n = 28, n = 54, respectively).<sup>10,15</sup> However, Arroyo-Novoa et al and Hyun et al found duration of IV opioid to be protective against IWS, despite significantly higher cumulative doses.<sup>9,16</sup> Proposed explanations were longer durations resulting in lower daily opioid doses, or cumulative doses having greater impact than durations on the

**Table 3.** Univariate and Multivariable Analyses of Candidate Risk Factors for Development of IWS.

Variable	Univariate Analysis			Multivariable Analysis		
	OR	95% CI	P-value	Adjusted OR	95% CI	P-value
Age	0.99	0.96-1.01	.35			
SAPS II	0.98	0.95-1.01	.18	0.96	0.93-0.999	.046
RASS, day 5 average	0.94	0.76-1.16	.54			
History alcohol abuse	1.02	0.28-3.73	.98			
History substance abuse	1.55	0.55-4.40	.41			
Duration of MV, days	1.09	1.04-1.13	<.0001			
ICU length of stay, days	1.09	1.04-1.14	.0002	1.05	0.99-1.11	.093
Cumulative IV opioid dose <sup>a,c</sup>	1.008	0.99-1.02	.069			
Cumulative IV benzodiazepine dose <sup>a,d</sup>	1.06	1.01-1.12	.032			
Cumulative dexmedetomidine dose <sup>b</sup>	1.008	1.003-1.014	.003			
Cumulative propofol dose <sup>a</sup>	1.002	1.001-1.004	.004			
Cumulative ketamine dose <sup>a</sup>	1.001	0.998-1.002	.67			
Cumulative duration IV opioid, days	1.11	1.06-1.17	<.0001	1.08	1.02-1.14	.005
Cumulative duration IV benzodiazepine, days	1.10	1.04-1.16	.001			
Cumulative duration dexmedetomidine, days	1.11	1.04-1.19	.002			
Cumulative duration propofol, days	1.11	1.04-1.18	.001			
Cumulative duration ketamine, days	1.12	0.96-1.30	.15			
Sedative type received						
Lorazepam	2.79	1.22-6.36	.01	3.02	1.12-8.15	.029
Opioid type received						
Hydromorphone	2.83	1.28-6.26	.01			

Abbreviations: BMI, body mass index; MV, mechanical ventilation; RASS, Richmond Agitation Sedation Scale; SAPS II, Simplified Acute Physiology Score II.

<sup>a</sup>For each 100 mg increase.

<sup>b</sup>For each 100 mcg increase.

<sup>c</sup>IV morphine equivalents.

<sup>d</sup>IV lorazepam equivalents.

development of tolerance. These speculations are in conflict with our findings. While patients in our IWS group received both significantly higher cumulative durations and cumulative doses of opioids and sedatives, as shown in [Supplemental Figures 2\(a\)-2\(e\) and 3\(a\)-3\(e\)](#), differences in average daily doses of each medication between groups were non-significant, whereas cumulative durations of all IV medications apart from ketamine remained significantly different, suggesting that duration of exposure may play a more prominent role than cumulative doses in development of IWS. The risk of prolonged exposures is also in accordance with findings in the pediatric population and current conceptual understandings of the development of opioid tolerance.<sup>22</sup>

Our results showed longer durations of MV increased the odds of IWS. Two studies conducted in surgical/trauma ICU patients showed similar results, with Arroyo-Novoa et al finding an 8% increased odds of IWS per additional day (95% CI, 1.02-1.15).<sup>9,10</sup> Cammarano et al found a significant association between ARDS and IWS.<sup>10</sup> Given all patients in our study had ARDS, a possible explanation for IWS development was more severe ARDS progression in the IWS group, however, P/F ratios indicated that ARDS severity actually improved over time in the IWS group ([Table 1](#)). Alternatively, survival in the non-IWS group was numerically but not statistically lower (57% vs 72%,  $P = .09$ ); it is possible that survival bias contributed to differences in IWS incidence, especially as symptom presentation can be delayed. This may partially explain the inverse association between SAPS II score and IWS in our final model.

### **Analgesic and Sedative Type, Prior Substance Abuse, Age**

Among IV sedatives, receipt of lorazepam was associated with increased odds of IWS in this study. Among BZDs, midazolam is generally preferred in ICU sedation due to its shorter half-life. The use of lorazepam has been associated with several negative outcomes, primarily delayed time to extubation and prolonged sedation.<sup>23,24</sup> When compared to subjects that received only midazolam, our lorazepam recipients trended towards longer durations of MV; longer durations of MV have been associated with IWS in both our and prior studies.<sup>9,10</sup>

In univariate analysis, receipt of hydromorphone was associated with increased odds of IWS. Due to the retrospective design of our study, we do not know the reason(s) for initiation of hydromorphone, however, current literature suggests transitioning to hydromorphone may have benefits in maintaining respiratory compliance and reducing sedative requirements.<sup>25</sup>

Previous studies of IWS excluded patients with a history of substance and/or alcohol abuse. Counter to Arroyo-Novoa et al, we did not find any statistically significant differences in odds of IWS in those with either prior substance or alcohol

abuse, however, our cohort contained a comparatively smaller proportion of patients with history of drug use (15% vs 35%), which may have limited our ability to detect these differences. Similarly, we did not find any associations between age and IWS, however, given that older age is a risk factor for severe COVID-19, we had a lower proportion of younger patients in our study.

Current approaches in IWS management include the addition of and/or transition to oral analgesic and sedative agents, and/or the gradual tapering of IV agents. However, given the findings of our study, exploration of alternative sedation strategies to reduce initial opioid exposures within the ICU population may be useful for future directions. For example, prior studies on opioid/sedative rotation and multimodal analgesia have showed significantly lower opioid and sedative requirements in ICU populations.<sup>26-30</sup> Additional studies of sequential sedation in ICU patients have found significantly lower risk of delirium, and reductions in duration MV and agitation.<sup>31,32</sup> However, further research is needed to better understand the utility of these alternative strategies with respect to IWS specifically.

Given the homogeneity of our patients, findings of this study may be useful to other ICU populations with similar levels of acuity. Additionally, Denver Health's sedation practices in COVID-19 ARDS patients appear similar to other institutions' in terms of cumulative dose requirements and agents used.<sup>3,5</sup>

Notable limitations of our study include a small sample size, as well as lack of a standardized institutional sedation, weaning, and/or withdrawal management protocol, allowing for variation in sedation practices and oral regimen initiation between patients. Unlike other studies that used predefined criteria to determine presence of IWS, we defined IWS based on receipt of a scheduled oral regimen after cessation of IV therapy, allowing for inter-physician variability in the recognition of IWS. However, as mentioned previously, there is currently no validated or standardized scoring tool to evaluate IWS in adults. It should be noted that standards of care for COVID-19 ICU patients evolved during the period from which our data were collected. While additional therapies likely became part of many patients' care part way through our data collection period, there were no meaningful differences in clinical markers such as duration of MV or hospital LOS when stratifying patient groups by their dates of implementation within our institution.

### **Conclusion**

COVID-19 ARDS patients with IWS experienced longer durations of MV, ICU LOS, and hospital LOS. Patients who received IV benzodiazepines, specifically lorazepam, and increased cumulative duration of IV opioids were positively associated with IWS. Prolonged and high dose exposures to these medications should be limited when possible. Alternative sedation strategies such as sequential sedation,

opioid rotation, and multimodal analgesia may have potential benefit in IWS prevention, however, current clinical data in this population are lacking. Additional prospective studies are needed to identify modifiable risk factors to prevent IWS.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

### Presentation of Work

The abstract was delivered as a pre-recorded presentation at the Society of Critical Care Medicine 51<sup>st</sup> Critical Care Congress. The abstract was included in Critical Care Medicine's January 2022 supplement publication.

### ORCID iDs

Melissa Vu Maffei  <https://orcid.org/0000-0002-4656-8764>  
Andy Kim, PharmD, BCCCP  <https://orcid.org/0000-0002-9890-5259>

### Supplemental Material

Supplemental material for this article is available online.

### References

- Pun BT, Badenes R, Heras La Calle G, et al. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. *Lancet Respir Med.* 2021;9(3):239-250. doi:10.1016/S2213-2600(20)30552-X.
- Devlin JW, Pandharipande PP. Do our sedation practices contribute to increased mortality in Coronavirus disease 2019-related acute respiratory distress syndrome? *Crit Care Med.* 2021;49:1579-1582. doi:10.1097/CCM.0000000000005094.
- Kapp CM, Zaeh S, Niedermeyer S, et al. The use of analgesia and sedation in mechanically ventilated patients with COVID-19 acute respiratory distress syndrome. *Anesth Analg.* 2020;131(4):e198-e200. doi:10.1213/ANE.0000000000005131.
- Balakrishna A, Walsh EC, Hamidi A, et al. An examination of sedation requirements and practices for mechanically ventilated critically ill patients with COVID-19. *Am J Health Syst Pharm.* 2021;78:1952-1961. doi:10.1093/ajhp/zxab202.
- Wongtangman K, Santer P, et al. Association of sedation, coma, and in-hospital mortality in mechanically ventilated patients with coronavirus disease 2019-related acute respiratory distress syndrome: a retrospective cohort study. *Crit Care Med.* 2021;49(9):1524-1534. doi:10.1097/CCM.0000000000005053.
- Riggi G, Zapantis A, Leung S. Tolerance and withdrawal issues with sedatives in the intensive care unit. *Crit Care Nurs Clin North Am.* 2016;28(2):155-167. doi:10.1016/j.cnc.2016.02.010.
- Jiang S, Petriceks AH, Burke H, Stern TA. Weaning from exogenous sedation in the era of COVID-19 infection: recommendations for sedation and its discontinuation. *Prim Care Companion CNS Disord.* 2020;22(4):20f02686. doi:10.4088/PCC.20f02686.
- Ego A, Halenarova K, Creteur J, Taccone FS. How to manage withdrawal of sedation and analgesia in mechanically ventilated COVID-19 patients? *J Clin Med.* 2021;10(21):4917. doi:10.3390/jcm10214917.
- Arroyo-Novoa CM, Figueroa-Ramos MI, Balas M, Rodriguez 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.000000000000089.
- Cammarano WB, Pittet JF, 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.
- Devlin JW, Skrobik Y, Gelinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med.* 2018;46(9):e825-e873. doi:10.1097/CCM.0000000000003299.
- Devlin JW, O'Neal HR Jr., Thomas C, et al. Strategies to optimize ICU liberation (A to F) bundle performance in critically ill adults with Coronavirus disease 2019. *Crit Care Explor.* 2020;2(6):e0139. doi:10.1097/CCE.000000000000139.
- Franck LS, Harris SK, Soetenga DJ, Amling JK, Curley MA. The withdrawal assessment tool-1 (WAT-1): an assessment instrument for monitoring opioid and benzodiazepine withdrawal symptoms in pediatric patients. *Pediatr Crit Care Med.* 2008;9(6):573-580. doi:10.1097/PCC.0b013e31818c8328.
- Ista E, van Dijk M, de Hoog M, Tibboel D, Duivenvoorden HJ. Construction of the Sophia observation withdrawal symptoms-scale (SOS) for critically ill children. *Intensive Care Med.* 2009;35(6):1075-1081. doi:10.1007/s00134-009-1487-3.
- Wang PP, Huang E, Feng X, et al. Opioid-associated iatrogenic withdrawal in critically ill adult patients: a multicenter prospective observational study. *Ann Intensive Care.* 2017;7(1):88. doi:10.1186/s13613-017-0310-5.
- Hyun DG, Huh JW, Hong SB, Koh Y, Lim CM. Iatrogenic opioid withdrawal syndrome in critically ill patients: a retrospective cohort study. *J Kor Med Sci.* 2020;35(15):e106. doi:10.3346/jkms.2020.35.e106.
- Taesotikul S, Dilokpattanamongkol P, Tangsujaritvijit V, Suthisisang C. Incidence and clinical manifestation of iatrogenic opioid withdrawal syndrome in mechanically ventilated patients. *Curr Med Res Opin.* 2021;37(7):1213-1219. doi:10.1080/03007995.2021.1928616.
- 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. <https://www.ncbi.nlm.nih.gov/pubmed/10776874>. Accessed May 24, 2021.

19. Globalrph. Opioid Analgesic Converter. <https://globalrph.com/medcalcs/opioid-conversions-calc-original-single-agent/>. Accessed July 16, 2021.
20. Clinicalc. *Equivalent Benzodiazepine Calculator*. <https://clinicalc.com/Benzodiazepine/>. Accessed July 16, 2021.
21. Jean-Roger Le Gall M. Simplified Acute Physiology Score (SAPS) II. <https://www.mdcalc.com/simplified-acute-physiology-score-saps-ii>. Accessed July 2, 2021.
22. Morgan MM, Christie MJ. Analysis of opioid efficacy, tolerance, addiction and dependence from cell culture to human. *Br J Pharmacol*. 2011;164(4):1322-1334. doi:10.1111/j.1476-5381.2011.01335.x.
23. Carson SS, Kress JP, Rodgers JE, et al. A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. *Crit Care Med*. 2006;34(5):1326-1332. doi:10.1097/01.CCM.0000215513.63207.7F.
24. Barr J, Zomorodi K, Bertaccini EJ, Shafer SL, Geller E. A double-blind, randomized comparison of i.v. lorazepam versus midazolam for sedation of ICU patients via a pharmacologic model. *Anesthesiology*. 2001;95(2):286-298. doi:10.1097/0000542-200108000-00007.
25. Kovacevic MP, Szumita PM, Dube KM, DeGrado JR. Transition from continuous infusion fentanyl to hydromorphone in critically ill patients. *J Pharm Pract*. 2020;33(2):129-135. doi:10.1177/0897190018786832.
26. Brown CGD, Riker R, Rolfe S, Fraser G. Opioid rotation in mechanically ventilated critically ill patients: a prospective exploratory study. *Crit Care Med*. 2018;46(1):470. doi:10.1097/01.ccm.0000528981.64716.e8.
27. Sanavia E, Mencia S, Lafever SN, et al. Sedative and analgesic drug rotation protocol in critically ill children with prolonged sedation: evaluation of implementation and efficacy to reduce withdrawal syndrome. *Pediatr Crit Care Med*. 2019;20(12):1111-1117. doi:10.1097/PCC.0000000000002071.
28. Neunhoeffer F, Hanser A, Esslinger M, et al. Ketamine infusion as a counter measure for opioid tolerance in mechanically ventilated children: a pilot study. *Paediatr Drugs*. 2017;19(3):259-265. doi:10.1007/s40272-017-0218-4.
29. Harkin M, Miller JL, Lim SY, et al. Conversion from continuous infusion fentanyl to continuous infusion hydromorphone in the pediatric intensive care unit. *Ann Pharmacother*. 2021;55:1439-1446. doi:10.1177/10600280211003170.
30. Garber PM, Droegge CA, Carter KE, Harger NJ, Mueller EW. Continuous infusion ketamine for adjunctive analgosedation in mechanically ventilated, critically ill patients. *Pharmacotherapy*. 2019;39(3):288-296. doi:10.1002/phar.2223.
31. Yang J, Zhou Y, Kang Y, et al. Risk factors of delirium in sequential sedation patients in intensive care units. *BioMed Res Int*. 2017;2017:3539872. doi:10.1155/2017/3539872.
32. Zhou Y, Jin X, Kang Y, et al. Midazolam and propofol used alone or sequentially for long-term sedation in critically ill, mechanically ventilated patients: a prospective, randomized study. *Crit Care*. 2014;18(3):R122. doi:10.1186/cc13922.