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International Analgesia and Sedation Weaning and Withdrawal Practices in Critically Ill Adults: The Adult Iatrogenic Withdrawal Study in the ICU*

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KEY WORDS:

iatrogenic; opioid; sedation; sedative; withdrawal

OBJECTIVES:

Iatrogenic withdrawal syndrome (IWS) associated with opioid and sedative use for medical purposes has a reported high prevalence and associated morbidity. This study aimed to determine the prevalence, utilization, and characteristics of opioid and sedative weaning and IWS policies/protocols in the adult ICU population.

DESIGN:

International, multicenter, observational, point prevalence study.

SETTING:

Adult ICUs.

PATIENTS:

All patients aged 18 years and older in the ICU on the date of data collection who received parenteral opioids or sedatives in the previous 24 hours.

INTERVENTIONS:

None.

MEASUREMENTS AND MAIN RESULTS:

ICUs selected 1 day for data collection between June 1 and September 30, 2021. Patient demographic data, opioid and sedative medication use, and weaning and IWS assessment data were collected for the previous 24 hours. The primary outcome was the proportion of patients weaned from opioids and sedatives using an institutional policy/protocol on the data collection day. There were 2,402 patients in 229 ICUs from 11 countries screened for opioid and sedative use; 1,506 (63%) patients received parenteral opioids, and/or sedatives in the previous 24 hours. There were 90 (39%) ICUs with a weaning policy/protocol which was used in 176 (12%) patients, and 23 (10%) ICUs with an IWS policy/protocol which was used in 9 (0.6%) patients. The weaning policy/protocol for 47 (52%) ICUs did not define when to initiate weaning, and the policy/protocol for 24 (27%) ICUs did not specify the degree of weaning. A weaning policy/protocol was used in 34% (176/521) and IWS policy/ protocol in 9% (9/97) of patients admitted to an ICU with such a policy/protocol. Among 485 patients eligible for weaning policy/protocol utilization based on duration of opioid/sedative use initiation criterion within individual ICU policies/protocols 176 (36%) had it used, and among 54 patients on opioids and/or sedatives \geq 72 hours, 9 (17%) had an IWS policy/protocol used by the data collection day.

CONCLUSIONS:

This international observational study found that a small proportion of ICUs use policies/protocols for opioid and sedative weaning or IWS, and even when these policies/protocols are in place, they are implemented in a small percentage of patients.

Withdrawal from opioids and sedatives administered under medical supervision is known as iatrogenic withdrawal syndrome (IWS) (1, 2). In the adult critically ill population, which routinely receives opioids and sedatives for supportive care, IWS prevalence has been reported to be between 17% and 100% depending on the study design and population examined (3–8). Risk factors associated with IWS include cumulative dose and duration of administration of 72 hours or more (3, 6, 7). Negative clinical outcomes have been associated with IWS, including prolonged mechanical ventilation and ICU length of stay (7).

Weaning opioids and sedatives through gradual dose reductions may be a strategy to minimize the risk of IWS in the ICU (9–12). Protocolized weaning of opioids and sedatives in pediatric and neonatal ICUs has been shown to decrease overall drug exposure and reduce IWS and ICU length of stay (9–11).

Despite what is known about the prevalence, risk factors, and effects of IWS in the pediatric and neonatal ICU populations, little has been published regarding opioid and sedative weaning and IWS practices currently employed in adult ICUs. In addition, methods used in the adult ICU population to monitor and assess IWS have not been adequately studied (6, 13). The aim of this study was to determine the prevalence, utilization, and characteristics of opioid and sedative weaning and IWS policies/protocols in the adult ICU population. We hypothesized that opioid and sedative weaning and IWS practices are not standardized and are infrequently employed in adult ICUs.

MATERIALS AND METHODS

Study Design

We conducted an international, multicenter, observational, 1-day point prevalence study. The study is registered with ClinicalTrials.gov (NCT04422808). Sites were recruited through an iterative process via professional networks, Listservs, a study website, and social media. The study was determined to be exempt by the Wilkes University Institutional Review Board (no. 116); each individual site was required to obtain local research ethics approval before study initiation. Study procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as most recently amended. We report study findings in accordance with the STrengthening the Reporting of Observational studies in Epidemiology checklist (14).

Study Population

Each participating ICU selected 1 day for data collection between June 1 and September 30, 2021. Criteria for enrollment included all patients aged 18 years or older in the ICU on the data collection date who received any parenteral opioids or sedatives in the previous 24 hours. Parenteral opioid or sedative use was defined as drug administration by either the IV, subcutaneous, intramuscular, or epidural routes. Enrolled patients were assessed for regularly dosed opioids or sedatives, which we defined as either continuous IV infusion, scheduled intermittent injection, or as needed doses with at least half of the possible doses from the previous 24 hours being administered.

Study Data and Clinical Information

All data were collected from the patient medical record and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at Wilkes University (15, 16). REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

Demographic data, opioid and sedative medication, and weaning and IWS assessment data were collected from the medical records of enrolled patients. Order sets, policies, and protocols were considered equivalent regarding their use to guide opioid and sedative utilization, weaning, and assessment and treatment of IWS. Weaning and IWS were not defined since each study site may have used their own definition. Thus, utilization of opioid-sedative weaning and IWS policies/protocols were self-reported by study sites.

Although the policies/protocols themselves were not evaluated by study investigators, the following data on these policies/protocols were reported by individual sites: provider(s) allowed to perform assessment, timing when weaning policy/protocol initiated, degree of opioid-sedative dose reduction, and IWS assessment tool(s) used. If an ICU reported having a weaning policy/protocol in place, patients admitted to that ICU were considered to be eligible for utilization of the policy/protocol if they met the timing for initiation criteria reported for the policy/protocol. Patients were coded as receiving mechanical ventilation if it was used on the date of data collection. Duration of mechanical ventilation and duration of ICU admission was the time up to the date of data collection.

Outcomes

The primary outcome was the proportion of patients who had parenteral opioids and/or sedatives weaned by an institutional policy/protocol on the data collection day. Secondary outcomes included the proportion of patients who were assessed for IWS with an institutional policy/protocol on the data collection day, proportion of patients in the ICU on the data collection day receiving any parenteral opioids and sedatives, and specific weaning practices.

Statistical Analysis

Data were summarized using frequencies and percentages for categorical variables and means with sd or medians with interquartile ranges (IQRs) for continuous variables depending on data distribution. Characteristics for ICUs and patients were grouped based on utilization of a policy/protocol for weaning or IWS and summarized since this was directly related to the primary outcome. Comparisons were made for ICU and patient demographic data based on the use of either a weaning or IWS policy/protocol. For comparisons between two parametric categorical variables either the chi-square or Fisher exact test was used, and for nonparametric continuous variables the Mann-Whitney *U* test was applied. Denominators are reported for categorical variable fields with missing data, and the number (*n*) is noted for continuous variable fields with missing data. Data entry for some fields was limited due to linked responses from other fields.

All descriptive and statistical analyses were performed using IBM SPSS Statistics version 28.0.0 (IBM, Armonk, NY). For comparisons between groups, the a priori alpha level was set at 5%.

RESULTS

A summary of hospital and patient enrollment is provided in **Figure 1**. Among 104 hospitals, 88 screened 2,437 patients admitted to 236 ICUs for use of any parenteral opioid and/or sedative in the previous 24 hours. Data for one hospital were not included in the final analysis due to a protocol violation where only one or two patients were enrolled from each ICU; thus, it appeared not all patients in this hospital's ICUs on the day of data collection were screened for opioid and sedative use. In addition, 22 patients were excluded due to missing data, and 4 due to age less than 18 years. This left 2,402 patients from 229 ICUs at 87 hospitals that were screened for enrollment, of which 1,506 received any parenteral opioid or sedative in the previous 24 hours and were enrolled.

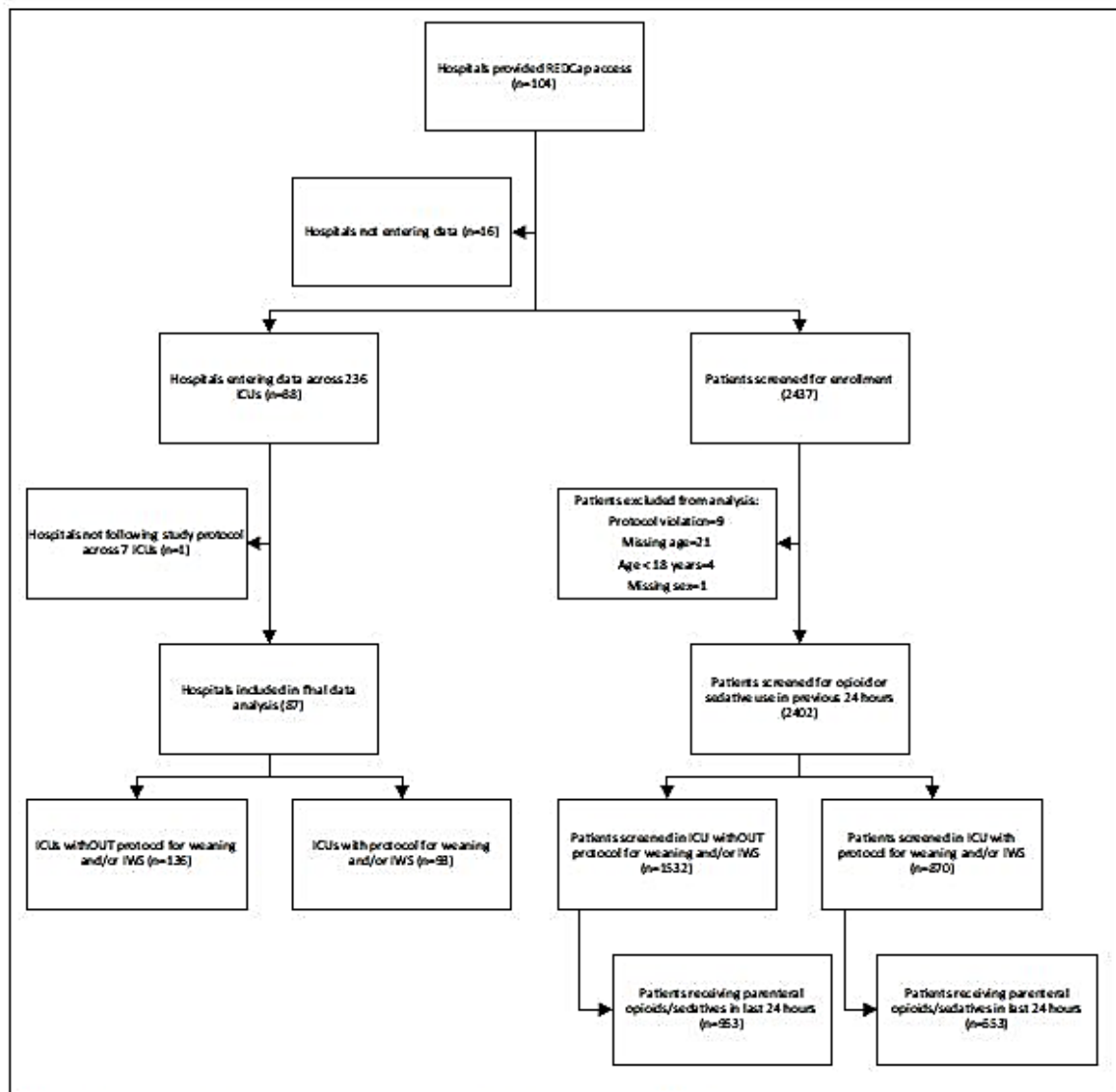


Figure 1. Flow diagram of hospital and patient enrollment. REDCap – Research Electronic Data Capture.

Study Sites Characteristics

Most hospitals (56.3%) were from the United States and the United Kingdom (**Fig. 2**), 60.9% were academic medical centers, 21.7% were community not-for-profit hospitals, 4.6% were community for-profit, and 13.8% were government or other nonpublic institutions. The median number of adult ICUs among all hospitals was 3 (IQR, 1–5), and the median number of total adult ICU beds per hospital was 46 (IQR, 23–75). The predominant ICU patient population was mixed medico- surgical (40.2%) with interprofessional bedside rounds occurring daily in the majority (53.3%) of ICUs (**Supplement Table 1**, <http://links.lww.com/CCM/H358>). Most participating ICUs (67.7%) employed a closed practice model (17, 18) and had a mean of 19 (sd ± 9) beds.

There were no significant differences in demographic data between ICUs that reported having an opioid-sedative weaning or IWS policy/protocol and those that did not, except a significantly higher percentage of ICUs that use a policy/protocol also used an order set to guide opioid-sedative therapy and daily interruption (**Supplement Table 1**, <http://links.lww.com/CCM/H358>).

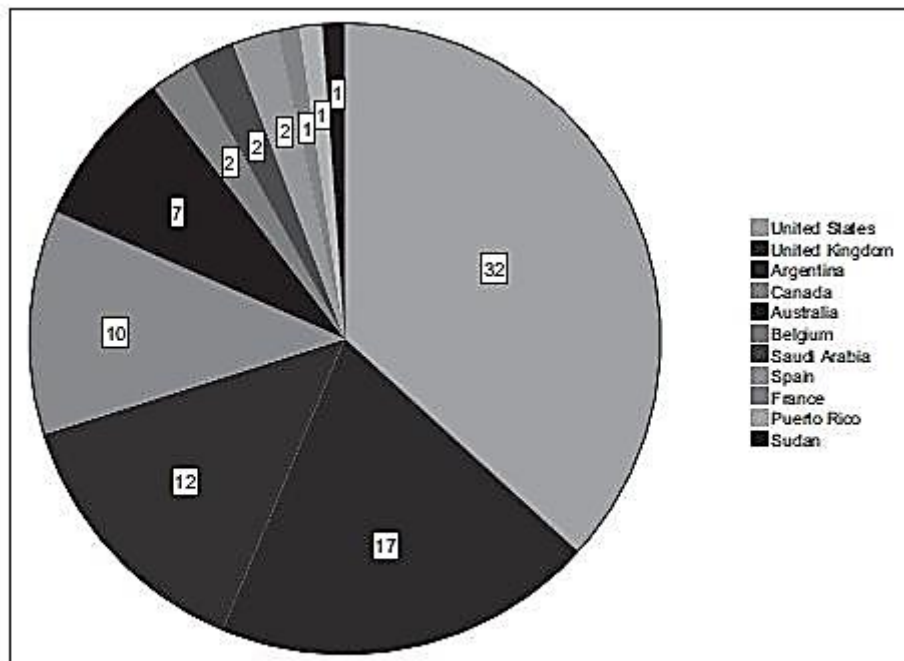


Figure 2. Number of study sites by country.

Patient Characteristics and Opioid-Sedative Use

The majority of patients (70.6%) screened for enrollment were from North America (**Fig. 3**). Demographic results for the 1,506 (62.7%) patients enrolled who received any parenteral opioid or sedative in the previous 24 hours are provided in **Supplement Table 2** (<http://links.lww.com/CCM/H358>). The mean age of patients was 56.4 (sd ± 16.0) years, 38.0% were female, 40.8% were admitted primarily for respiratory disease, 12.9% were using opioids before admission, and 29.8% had a positive PCR test for COVID-19. On the day of data collection, the median duration of ICU stay was 6 (IQR; 2–14) days, 30.6% had active

acute respiratory distress syndrome, and 74.4% were mechanically ventilated. There was a significant imbalance in various ethnic groups among patients admitted to ICUs that reported having or not having an opioid-sedative weaning or IWS policy/protocol. Also, patients in ICUs that use a policy/protocol were admitted for trauma more frequently and spent more time on mechanical ventilation, while patients in those that do not use a policy/protocol were more often admitted for circulatory system diseases.

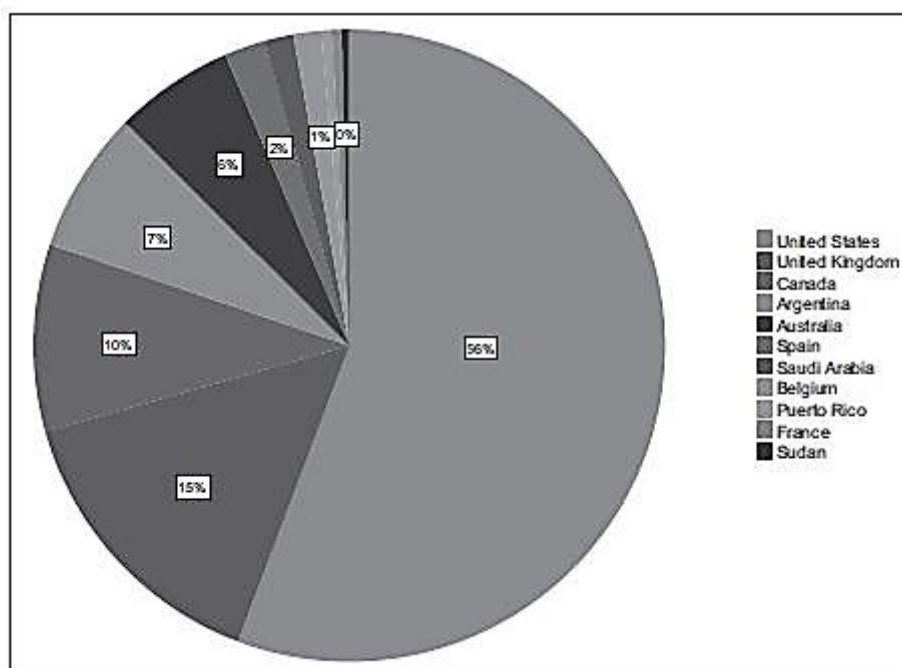


Figure 3. Patients screened for enrollment by country.

TABLE 1.
Opioid/Sedative Practices Among Patients Based on ICU Policy/Protocol Presence

Practice	ICU With Opioid-Sedative Weaning or Iatrogenic Withdrawal Syndrome Policy/Protocol		p
	No (n = 953)	Yes (n = 553)	
Receiving regularly dosed opioids, n (%)	817 (85.7)	488 (88.2)	0.166
Receiving regularly dosed sedatives, n (%)	751 (78.8)	400 (72.3)	0.004
Receiving regularly dosed opioids and sedatives	613/951 (64.5%)	335/553 (60.6%)	0.125
Opioid-sedative daily interruption order set being used	199/465 (42.8%)	175/377 (46.4%)	0.293
Opioid-sedative dose reduced in previous 24 hr	336/700 (48.0%)	186/401 (46.4%)	0.605
Opioid-sedative percent dose reduction in previous 24 hr			
Less than 10%	20/336 (6.0%)	6/186 (3.2%)	0.170
10%–20%	61/336 (18.2%)	43/186 (23.1%)	0.174
21%–30%	46/336 (13.7%)	36/186 (19.4%)	0.089
31%–50%	107/336 (31.8%)	52/186 (28.0%)	0.355
Greater than 50%	153/336 (45.5%)	80/186 (43.0%)	0.578
Enteral opioids/sedatives began in previous 24 hr	114/700 (16.3%)	80/402 (19.9%)	0.129

Among enrolled patients 1,305 (86.7%) received regularly dosed opioids, 1,151 (76.4%) received regularly dosed sedatives, and 950 (62.1%) received regularly dosed opioids and sedatives (**Table 1**). Thus, among the 1,506 patients enrolled 201 did not receive regularly dosed opioids, and 355 did not receive regularly dosed sedatives.

Opioid and Sedative Weaning Policies/Protocols

On the day of data collection, among all participating ICUs, a weaning policy/protocol was used in 176 of the 1,506 (11.7%) patients enrolled. Among enrolled patients, 521 (34.6%) were admitted to 90 (39.3%) ICUs with an opioid-sedative weaning policy/protocol. In ICUs with a weaning policy/protocol in place, it was used in 33.8% (176/521) of patients on the day of data collection (**Table 2**). Although clinical criteria to describe appropriateness for initiation of a weaning policy/protocol were not assessed, 485 (93.1%) patients admitted to ICUs with a weaning policy/protocol were eligible for policy/protocol initiation based on their duration of opioid/sedative use. Therefore, the policy/protocol was being used in 36.3% (176/485) of patients who met the criterion related to duration of opioid/sedative use on the day of data collection.

IWS Policies/Protocols

Among all participating ICUs, a policy/protocol for IWS was being used in 9 of the 1,506 (0.6%) patients enrolled. A total of 97 (6.4%) enrolled patients were admitted to 23 (10.0%) ICUs with an IWS policy/protocol. In ICUs with an IWS policy/protocol in place, it was used in 9.3% (9/97) of patients on the day of data collection. There were 55.7% (54/97) of patients in these ICUs who had been receiving parenteral opioids or sedatives for 72 hours or more by the day of data collection, which has been associated with IWS risk (3, 6). Although clinical criteria to describe appropriateness for initiation of an IWS policy/protocol were not assessed, 16.7% (9/54) of patients who received opioids or sedatives for 72 hours or more were utilizing the policy/protocol on the day of data collection.

Weaning and IWS Practices

ICUs with weaning policies/protocols in place generally delegate the responsibility of patient assessment to nurses and physicians, followed by pharmacists and other providers (**Table 3**). Also, the policies/protocols in the majority of ICUs do not define when to initiate weaning, and most that do define a time indicate less than 72 hours after beginning opioids or sedatives.

The policies/protocols in the majority of ICUs use an assessment scale or tool to determine the degree of weaning, while about one-quarter use a percent or absolute dose reduction, or do not specify.

Among ICUs using an IWS policy/protocol, 13 (56.5%) incorporated an IWS assessment tool: six used the Opioid and Benzodiazepine Withdrawal Score, one the Sophia Observation Symptoms Scale, one the Sophia Benzodiazepine and Opioid Withdrawal Checklist, and five an institutional tool.

TABLE 2.
ICU Weaning Policy/Protocol Initiation Criteria and Patient Eligibility and Use

Duration of Opioid/Sedative Use Initiation Criterion ^a	Patient Duration of Opioids or Sedatives ^b				Total (n = 521)	Patients Eligible Based on Initiation Criterion (n = 485) ^c	Patients in Which Policy/Protocol Used (n = 176) ^d
	< 24 hr (n = 133)	24 to < 72 hr (n = 95)	72 to < 96 hr (n = 50)	≥ 96 hr (n = 243)			
< 24 hr	36	18	14	80	148	148 (100%)	57 (38.5%)
24 to < 72 hr	24	19	6	36	85	61 (71.8%)	44 (72.1%)
72 to < 96 hr	1	5	0	2	8	2 (25%)	0 (0%)
≥ 96 hr	1	2	3	9	15	9 (60%)	2 (22.2%)
Not defined	71	51	27	116	265	265 (100%)	73 (27.5%)

^aSite investigators were asked how long after beginning regularly doses opioids or sedatives their ICU's policy/protocol for weaning analgesics/sedatives was indicated to be initiated.

^bFor each patient enrolled site investigators were asked how long the patient had been receiving regularly dosed opioids and/or sedatives.

^cPatients in the ICU on the data collection day who met the respective criterion in the Duration of Opioid/Sedative Use Initiation Criterion column.

^dPatients among those eligible in each Duration of Opioid/Sedative Use Initiation Criterion who had the policy/protocol implemented by the data collection day.

Comparison of Opioid and Sedative Utilization Among ICUs

Significantly more patients in ICUs without an opioid-sedative weaning or IWS policy/protocol received regularly dosed sedatives (Table 1). There was no significant difference in use of an opioid-sedative daily interruption order set, opioid-sedative dose reduction in the 24 hours before data collection, percent dose reduction, or initiation of enteral opioids or sedatives between patients in an ICU with an opioid-sedative weaning or IWS policy/ protocol and those in an ICU without a policy/protocol.

DISCUSSION

This international point prevalence study describes current opioid-sedative weaning and IWS management practices in adult ICUs. The results show that opioid-sedative weaning and IWS policies/protocols are not prevalent and are infrequently employed in adult ICUs. This is despite the fact that more than three-quarters of the patients who received parenteral opioids or sedatives had them provided on a regularly dosed basis, with more than two-thirds receiving them as continuous IV infusions. Also, the results demonstrate that in ICUs with a policy/protocol in place about one in three patients who met the ICU's duration of opioid/sedative use criterion for weaning policy/protocol initiation, and one in six who were at risk of IWS due to receiving opioids or sedatives for 72 hours or more (3, 6), had the policy/protocol used at the time of data collection. Finally, one-quarter of ICUs utilizing a weaning policy/protocol do not specify the degree of opioid-sedative weaning, and the majority of ICUs with a weaning policy/protocol do not specify when to initiate the policy/protocol.

This study also found that almost two-thirds of patients admitted to adult ICUs received parenteral opioids or sedatives in the 24 hours before data collection. This provides an estimate of the current prevalence of parenteral opioid and sedative use in critically ill adults. Utilization of parenteral opioids and sedatives in the current study was similar to that previously reported (19, 20).

TABLE 3.
ICU Protocolized Weaning Practices

Practice Within ICUs	ICU With Opioid-Sedative Weaning Policy/ Protocol (n = 90)
Provider allowed to perform weaning assessment, n (%)	
Nurse	77 (85.6)
Physician	69 (76.7)
Pharmacist	14 (15.6)
Other	11 (12.2)
When weaning protocol indicates it should be used after opioid-sedative begun, n (%)	
< 24 hr	20 (22.2)
24 to < 72 hr	12 (13.3)
72 to < 96 hr	8 (8.9)
96 hr or more	3 (3.3)
Not defined	47 (52.2)
Degree of weaning	
Based on assessment scale/tool, n (%)	48 (53.3)
Percent dose reduction, n (%)	23 (25.6)
Median percent reduction (interquartile range)	50 (25-50)
Absolute dose reduction, n (%)	22 (24.4)
Does not specify, n (%)	24 (26.7)
Other, n (%)	15 (16.7)

Standardization of analgesia and sedation practices in the adult ICU utilizing protocols, including daily sedation interruption, is recommended by clinical practice guidelines and has demonstrated improved patient outcomes (21). Current guidelines do not offer insight about best practices for weaning opioids and sedatives or for assessing IWS in adult ICU patients. Current data about weaning protocols and IWS management are largely derived from the pediatric population. Utilization of such protocols in the pediatric population has been shown to decrease exposure to opioids and benzodiazepines, facilitate more calm and awake days, reduce the occurrence of IWS, and shorten hospital stays (22–24). The results of the current study show that ICUs utilizing an opioid-sedative order set, including daily interruption, often incorporate a policy/protocol for opioid-sedative weaning or IWS assessment; however, consistent with other reports, the availability of such policies/protocols does not guarantee their use in individual patients (25, 26). Policies/protocols for opioid-sedative weaning and IWS should be used along with clinical assessment of individual patients during interprofessional rounds, and not implemented strictly based on generalized predetermined parameters. Additional research in critically ill adults is needed that focuses on enhancing adherence to available policies/protocols and measuring their clinical benefits when incorporated at the bedside.

Interestingly, our results show that more than half of the ICUs that use an IWS policy/protocol incorporate an IWS assessment tool. Although several tools for assessment of IWS have been validated in critically ill children, none have been validated in the adult ICU population. The Withdrawal Assessment Tool-1 was tested in critically ill adults and demonstrated low sensitivity and specificity, leading the authors to conclude that it is not

useful to assess IWS in the adult ICU (27). Until a valid tool is available, it is difficult to provide a rigorous standardized approach to IWS assessment, and this may have contributed to the results reported from the current study. This represents another important gap that warrants further investigation.

Although this study included data from a large number of hospitals in multiple countries, there are several limitations. Data from many countries were provided by a small number of institutions, which limits generalizability of the data for those countries. In addition, data provided by institutions may not necessarily be representative of the practice within a particular country or geographic region. There also may have been bias in study site participation based on the recruitment methods used, with limited participation of sites whose investigators may not utilize Listservs, internet resources, or social media to identify opportunities for participation in multicenter research. Another important study design limitation is that reasons for the abrupt discontinuation of opioids and sedatives, and patient clinical criteria for readiness to wean, were not collected. Lack of data on why opioids and sedatives were abruptly discontinued, and on the clinical readiness of individual patients for weaning, regardless of policy/protocol triggers, could have biased the results when there may have been clinically justifiable reasons for acutely discontinuing these agents and not initiating weaning per policy/protocol triggers. While the terms “weaning” and “IWS” were clearly contextually tied to the use of analgesics and sedatives in the study protocol and case report form, the terms were not specifically defined for site investigators. This limitation may have led to bias in sites indicating if they used a weaning or IWS policy/protocol. An additional limitation is that only 24 hours of opioid and sedative data were collected at one point in time. Although this approach in study design made its completion more feasible, longitudinal data collection would have captured data that better represented the entire ICU stay of patients. Another limitation is that nearly 30% of included patients had a positive PCR test for COVID-19, and published reports suggest that these patients require higher cumulative doses of opioids and sedatives for longer durations, often with the need for more than one agent, compared to non-COVID-19 admissions (28–32). Inclusion of these patients may have biased the results, especially duration of opioid and sedative use, receipt of regularly dosed agents, dose reduction, and initiation of enteral agents. Finally, data were only captured for patients who received parenteral opioids or sedatives. Although we do report on those patients who began enteral opioids and/or sedatives in the 24 hours before data collection, those who were administered only nonparenteral agents, or who received both parenteral and nonparenteral agents, may have been utilizing weaning or IWS policies/protocols, but were not represented in the results of this study.

CONCLUSIONS

Very few ICUs utilize an opioid-sedative weaning or IWS policy/protocol, and for those that do these policies/ protocols are implemented in a small proportion of patients. This is despite that more than three-quarters of adult ICU patients received regularly dosed opioids or sedatives in the 24 hours before data collection. These results demonstrate that there is underutilization of opioid-sedative weaning and IWS assessment practices in a significant proportion of critically ill adults. This is likely related to the absence of standardized methods for opioid-sedative weaning and a validated IWS assessment tool for critically ill adults. Such methods and a tool are required components for any effort trying to establish the clinical value of opioid-sedative weaning and IWS strategies. Current guidelines should advocate for

research regarding valid methods and tools to guide opioid and sedative weaning and IWS practices, including the prevalence, assessment, prevention, and treatment of IWS, and clinicians should be aware of the potential risk of IWS with regularly dosed opioids and sedatives.

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