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Protocolized Sedation versus Usual Care in Pediatric Patients Mechanically Ventilated for Acute Respiratory Failure: A Randomized Clinical Trial

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Abstract

Importance—Protocolized sedation improves clinical outcomes in critically-ill adults, but its effect in children is unknown.

Objective—To determine whether critically-ill children managed with a nurse-implemented, goal-directed sedation protocol (*RESTORE*) would experience fewer days of mechanical ventilation than patients receiving usual care.

Design, Setting, and Participants—Cluster-randomized trial conducted in 31 U.S. Pediatric Intensive Care Units (PICUs). Children (n=2449; mean age 4.7 years, range 2 weeks to 17 years) mechanically ventilated for acute respiratory failure were enrolled 2009–2013 and followed until 72 hours after opioids were discontinued, 28 days, or hospital discharge.

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*The Randomized Evaluation of Sedation Titration for Respiratory Failure (*RESTORE*) study investigators are listed in the Supplementary Online Content.

Author Contributions:

Drs. Curley and Wypij had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of data analyses.

Interventions—Intervention PICUs (17 sites, n=1225 patients) managed sedation using a protocol that included targeted sedation, arousal assessments, extubation readiness testing, sedation adjustment every 8 hours, and sedation weaning. Control PICUs (14 sites, n=1224 patients) managed sedation per usual care without a protocol.

Main Outcome and Measures—The primary outcome was duration of mechanical ventilation. Secondary outcomes included time to recovery from acute respiratory failure, duration of weaning from mechanical ventilation, neurological testing, PICU and hospital lengths of stay, in-hospital mortality, sedation-related adverse events, sedative exposure including measures of wakefulness, pain, and agitation, and occurrence of iatrogenic withdrawal.

Results—Duration of mechanical ventilation was not statistically significantly different between the two groups (median; interquartile range: intervention: 6.5 days; 4.1–11.2 vs. control: 6.5; 3.7–12.1). Sedation-related adverse events including inadequate pain and sedation management, clinically significant iatrogenic withdrawal, and unplanned endotracheal tube/invasive line removal were not statistically significantly different between the two groups. Intervention patients experienced more post-extubation stridor (7% vs. 4%; P=0.03) and fewer stage 2+ immobility-related pressure ulcers (<1% vs. 2%; P=0.001). In exploratory analyses, intervention patients had fewer days of opioid administration (median; interquartile range: 9; 5–15 vs. 10; 4–21; P=0.01), were exposed to fewer sedative classes (2; 2–3 vs. 3; 2–4; P<0.001), and were awake and calm for a greater percentage of study days while intubated (86%; 67–100% vs. 75%; 50–100%; P=0.004), than control patients. However, patients in the intervention group had a greater percentage of days with any report of a pain score ≥4 (50%; 27%-67% vs. 23%; 0–46%; P<0.001) and any report of agitation with a State Behavior Scale score of +1/+2 (60%; 33–80% vs. 40%; 13–67%, P=0.003), than control patients.

Conclusions and Relevance—Among children undergoing mechanical ventilation for acute respiratory failure, the use of a nurse-implemented, goal-directed sedation protocol compared with usual care did not reduce the duration of mechanical ventilation. Exploratory analyses of secondary outcomes suggest a complex relationship between wakefulness, pain, and agitation.

Trial Registration—NCT00814099.

Keywords

Cluster-randomized trial; nurse-led therapy; goal-directed therapy; trajectory of illness; algorithm; extubation readiness; analgesia; pain; agitation; withdrawal; State Behavioral Scale; Withdrawal Assessment Tool–Version 1; pediatric intensive care

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Ensuring the safety and comfort of critically-ill infants and children supported on mechanical ventilation is integral to the practice of pediatric critical care. [1] Although sedation therapy benefits young patients who cannot understand the imperative nature of invasive life-sustaining therapies, sedative use is also associated with untoward side effects. [2] Specifically, opioids and benzodiazepines commonly used for pediatric sedation may impair bedside neurological assessment, depress spontaneous ventilation, and prolong mechanical ventilation. Over time, drug tolerance develops which may precipitate iatrogenic withdrawal syndrome when sedation therapy is no longer necessary. [3,4]

Numerous studies in adult critical care support a minimal, yet effective, approach to sedation management. [5] Sedation goals for mechanically ventilated adults have shifted from an unresponsive state to a calm, easily aroused, readily evaluated patient. [6] Studies in adult patients evaluating targeted sedation, [7] daily interruption and/or titration of sedation, [8] pairing of spontaneous awakening with breathing [9] and no sedation [10] have reported improved clinical outcomes, including decreased length of mechanical ventilation when compared with usual care.

In contrast, few data inform sedation practices in pediatric critical care, and international studies describe significant practice variation. [1,11,12] Given unique biobehavioral differences, knowledge generated in adult critical care may not translate to the care of critically-ill children. We conducted a multicenter cluster-randomized clinical trial to test the effect of a nurse-implemented, goal-directed sedation protocol on clinical outcomes in pediatric patients with acute respiratory failure. Our primary aim was to determine whether critically-ill children managed with a nurse-implemented goal-directed sedation protocol would experience fewer days of mechanical ventilation than patients receiving usual care.

METHODS

Study Design

This unblinded multicenter cluster-randomized clinical trial conducted in the U.S. tested an intervention that changed how the intensive care team worked together to manage a patient's level of sedation on a day-to-day basis. To avoid patient-level contamination from this systems-level organizational change in sedation practice, the unit of randomization was the pediatric intensive care unit (PICU), the unit of analysis was the patient, and we accounted for site effects. [13,14]

PICUs were recruited from the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Eligible PICUs did not have a sedation protocol in place, showed evidence of nursing and physician leadership support, agreed to the research design where approximately half of the PICUs would be randomized to the Randomized Evaluation of Sedation Titration for Respiratory Failure (*RESTORE*) intervention as a research protocol or to continued usual care, and could enroll a minimum of 3 patients per month. We obtained approval from each institutional review board, as well as written informed consent from the legal guardian of each enrolled patient.

During the baseline phase, all PICUs implemented the same pediatric-specific standard, valid, and reliable pain, sedation, and iatrogenic withdrawal assessment instruments. The pain scale used depended upon the patient's age and verbal/cognitive capacity: the Face, Legs, Activity, Cry, Consolability (FLACC) scale in nonverbal children 0 to 6 years of age, the individualized numeric rating scale (INRS) in nonverbal cognitively impaired children age 6 and older, and the Wong-Baker Faces Pain Scale (WBFPS) in verbal children age 3 and older. [15–17] All pain scales range 0–10 with higher scores indicating more pain. Level of sedation in intubated patients was assessed using the State Behavioral Scale (SBS). [18] SBS scores range from -3 (unresponsive) to +2 (agitated), with a preferred SBS of -1 (responsive to gentle touch or voice). In patients receiving neuromuscular blockade, pain/agitation was

judged to be present when a patient demonstrated a ≥20% increase in heart rate or blood pressure when stimulated. All patients weaning from ≥5 days of opioids were monitored for opioid or benzodiazepine withdrawal symptoms using the Withdrawal Assessment Tool-1 (WAT-1). [19] The WAT-1 scale ranges 0–12 with higher scores indicating more withdrawal symptoms.

Prior to randomization, PICUs were given a copy of the protocol that described the intervention only in general terms. PICUs provided baseline data that allowed a comparison of available patient population and major organizational factors (eTables 1 and 2). PICUs were grouped by the number of eligible patients: small, medium, and large. The study began with 22 PICUs that were stratified by size and, within each stratum, assigned to the intervention or control group via computer-generated random numbers so that approximately half were assigned to each group. To increase enrollment rates one year after study initiation, 9 PICUs were added following the same procedures. Anticipating lower consent rates in the intervention group, where parents consented for study treatment rather than data collection alone, we randomized more PICUs to the intervention group.

Patients 2 weeks to 17 years of age receiving invasive mechanical ventilation for acute airways and/or parenchymal lung disease were eligible. We excluded patients whose length of mechanical ventilation was unlikely to be altered by sedation management, for example, patients only ventilated for post-operative care and/or those expected to be extubated within 24 hours (eTable 3). PICUs screened all intubated patients daily. Guardians were approached for consent within 24 hours of the patient meeting study criteria with the goal of protocol initiation within 48 hours.

Sedation Protocol

The *RESTORE* protocol includes interprofessional team training and the use of a nurse-implemented, goal-directed comfort algorithm to guide sedation therapy (Supplementary Online Content). Core elements included daily team discussion of the patient's trajectory of illness (acute, titration, or weaning phase); prescribing a SBS target per phase of illness; modified arousal assessment if responsive only to noxious stimuli (SBS=-2) or full arousal assessment if unresponsive to stimulation (SBS=-3) in the titration/weaning phases; daily extubation readiness test (ERT) when spontaneously breathing with an oxygenation index ≤6; adjustment of sedatives based on phase of illness at least every 8 hours; discontinuation of opioids and benzodiazepines when no longer necessary (if exposed <5 days) or weaned per target WAT-1 (if exposed ≥5 days); and a written sedation weaning plan when transferred out of the PICU.

Patients meeting ERT criteria underwent testing each morning. [20] ERT results were discussed during multidisciplinary rounds. If a patient failed the ERT, the patient was returned to pre-test ventilator settings and re-tested the next morning. If the patient failed the ERT because of excessive sedation, the team weaned sedation and retested the patient. If a patient passed the ERT, the team extubated the patient within 6 hours or chose to keep the patient intubated for non-pulmonary reasons. Post-extubation pulmonary management was not protocolized.

The protocol delineated how sedatives, typically prescribed in the PICU, were managed. Primary sedative agents included morphine and midazolam. [11] Fentanyl was recommended as a primary agent for patients with hypotension or reactive airways disease. Morphine was selected as the primary opioid because, compared with fentanyl, it has a longer duration of action and some sedative properties. In addition, tolerance is thought to occur more rapidly with the short-acting opioid fentanyl. [3] Secondary sedative agents included dexmedetomidine or propofol to facilitate extubation and clonidine, pentobarbital, or ketamine when unresponsive to primary agents. Clonidine was also recommended to manage iatrogenic withdrawal with methadone recommended only if WAT-1 scores continued to be above target. Nurses used the algorithm with a standardized orderset to manage sedation per phase of illness and prescribed SBS.

Post-randomization, coinvestigators from each intervention PICU attended a start-up meeting where they received the algorithm and training materials that included discipline-specific slide packages, digital file of an arousal assessment, pocket reminder cards, and bedside booklets. Site coinvestigators then customized the training materials for their PICU and conducted training that included lectures, informal case discussions, and self-learning packages. All clinicians involved in the management of mechanically ventilated patients (physicians, clinical pharmacists, and nursing staff) were trained and were required to demonstrate understanding of the intervention by completion of a discipline-specific, scenario-based post-test. Respiratory therapists were trained on evaluating patient readiness for extubation and synchronizing the ERT with an evaluation of the patient's SBS. Training was also embedded into unit orientation programs to accommodate new and rotating staffs. On average, PICUs reported training 164±99 (mean ± standard deviation) staff members, primarily nurses (114±71). This required spending approximately 1.4±0.9 hours per person on initial protocol training followed by an additional 1.4±1.1 hours per person in maintenance training through the course of the study.

Control PICUs did not receive a copy of the algorithm and managed sedation per usual care without a protocol. Sedatives were selected, prescribed, and titrated at the discretion of the medical team. No recommendations were made for extubation readiness testing.

Outcome Measures and Statistical Analysis

The primary outcome was duration of mechanical ventilation, beginning on Day 0 at the time of endotracheal intubation, initiation of assisted breathing for patients with tracheostomies, or PICU admission for patients intubated at an outside hospital, and continuing until the first time the endotracheal tube was continuously absent for at least 24 hours or, in patients with tracheostomies, the first time pressure support was <5 cm H2O (continuous or bi-level) for at least 24 hours. Patients were assigned 28 days if they remained intubated or were transferred or died prior to Day 28 without remaining extubated for >24 hours, therefore making the primary outcome equivalent to ventilator- [21] free days. [21]

All secondary outcomes were selected *a priori* and included time to recovery from acute respiratory failure, duration of weaning from mechanical ventilation, neurological testing, PICU and hospital lengths of stay, in-hospital mortality, sedation-related adverse events,

sedative exposure, and occurrence of iatrogenic withdrawal (eTable 4). Sedative exposure and sedation outcomes included measures of wakefulness, pain, and agitation; specifically, percentage of study days awake and calm (daily modal SBS=-1 [responsive to gentle touch or voice] or 0 [awake and able to calm]), days to first awake/calm, percentage of study days with modal pain score <4, and percentage of study days with any episode of pain (highest daily pain score ≥4) or agitation (highest daily SBS=+1/+2 [restless and difficult to calm/ agitated]).

Sedation-related adverse events were also defined *a priori* and prospectively monitored [22](eTable 4). These included inadequate pain management (pain score>4 [or pain assumed present if receiving neuromuscular blockade] for 2 consecutive hours), inadequate sedation management (SBS>0 [or agitation assumed present if receiving neuromuscular blockade] for 2 consecutive hours), clinically significant iatrogenic withdrawal in patients weaning from ≥5 days of opioids (rescue therapy to manage an increase in WAT-1 symptoms), extubation failure (reintubation within 24 hours), post-extubation stridor, unplanned extubation, unplanned removal of any invasive tube, ventilator-associated pneumonia, catheter-associated bloodstream infection, immobility-related stage 2+ pressure ulcers, and new tracheostomy.

The primary analysis compared the duration of mechanical ventilation in intervention vs. control patients using Kaplan-Meier curves and proportional hazards regression adjusting for age group (2 weeks to 1.99 years, 2.00 to 5.99 years, 6.00 to 17.99 years), Pediatric Risk of Mortality (PRISM) III-12 score, [23] and Pediatric Overall Performance Category (POPC)>1 [24] at enrollment and accounting for PICU as a cluster variable with generalized estimating equations. [25] Exploratory analyses of secondary outcomes used logistic, multinomial logistic, cumulative logit, linear, and Poisson regression accounting for PICU as a cluster variable using generalized estimating equations for binary, nominal, ordinal, continuous, and rate variables, respectively. Statistical analyses were performed with SAS software (Version 9.4, SAS Institute), using two-sided 0.05 level tests.

A priori, the study team determined that a 20% reduction in the duration of mechanical ventilation, or a hazard ratio of 1.25, was clinically important for patients managed with the sedation protocol and plausible based on our pilot study. [26] Assuming independent observations, proportional hazards between groups, and that up to 15% of patients would not be successfully extubated by Day 28, [26,27] 1050 patients were required for a two-sided 0.05 level log-rank test to achieve 90% power to detect a 20% reduction assuming three interim analyses to assess efficacy or futility using an O'Brien-Fleming [28] stopping rule (East, Version 5.3, Cytel Statistical Software). To account for the intraclass correlation coefficient (ICC) in our cluster-randomized design and using ICC=0.01 from previous experience [26,27] and conservatively assuming 22 sites, 1990 patients were required. [29,30] We chose 2448 patients as our target sample size to guarantee 90% power to detect a 20% reduction in length of ventilation controlling for patients not successfully extubated by Day 28, three formal interim analyses, and modest within-site correlations. This allowed for moderate site-to-site variability in cluster sizes and adjustment for age group, PRISM III-12 score, and POPC>1.

Study Oversight

Case report forms were designed to capture and allow compliance monitoring of core elements of the study protocol. In the intervention group, site coinvestigators rounded daily on each patient, separately from clinical rounds, to monitor patient safety, adverse events, and protocol compliance. Monthly compliance reports provided clinical teams with feedback on their sedation management performance. In the control group, auditors observed for the use of any sedation protocol during site visits. All sites participated in yearly individual site calls to review their study performance.

An independent Data and Safety Monitoring Board, appointed by the National Heart, Lung, and Blood Institute, oversaw all aspects of the trial, including performance, data quality, safety, and ethics. The board monitored adverse events, protocol adherence, and potential early stopping for efficacy or futility.

RESULTS

Characteristics of Study Units and Participants

Thirty-one PICUs participated (Figure 1; eTables 1 and 2). From June 2009 through December 2013, 2449 patients were enrolled, 1225 from 17 intervention sites and 1224 from 14 control sites. The percentage of intubated patients who were eligible was not statistically significantly different between groups (intervention 11% vs. control 13%; P=0.09). Consent rates were lower in the intervention PICUs (72% vs. 84%; P=0.01). Time from intubation to enrollment was shorter in the intervention PICUs (median; interquartile range: 21 hours; 12–31 vs. 24; 16–39; P=0.002). Twenty-five patients were withdrawn from the intervention group: 10 parents withdrew full consent for the protocol and data collection, 8 parents withdrew consent for the protocol but allowed continued data collection, and 7 attending physicians opted to manage patients off protocol. Data from the 15 withdrawn patients with parental consent for data collection are included in the analysis.

Baseline patient characteristics were not statistically significantly different between the two groups except the intervention group enrolled more patients <2 years of age and more patients with bronchiolitis. In this youngest age group, intervention patients had a lower predicted risk of mortality compared to control patients (median; interquartile range: 1.7; 0.7–4.9 vs. 3.8; 1.3–9.5; P=0.003; Table 1). The most prevalent diagnoses in both groups included pneumonia, bronchiolitis, and acute respiratory failure due to sepsis. Levels of oxygenation on Day 1 and early neuromuscular blockade use were not statistically significantly different between groups.

Protocol Fidelity

At enrollment, 1155 intervention patients (94%) were receiving a combined sedation strategy of opioids and benzodiazepines, while an additional 43 patients (4%) were transitioned to this strategy within 1 day (median; interquartile range: 1–3 days). Compliance with pain assessments did not differ by group but sedation and withdrawal assessments were completed more frequently in the intervention group (pain: 89% vs. 84%; P=0.80; sedation: 85% vs. 69%; P=0.01; withdrawal: 65% vs. 56%; P=0.03; eTable 5).

Compliance with elements of the sedation protocol ranged from 71 to 100% of eligible study days and 86 to 98% of patients (eTable 6). The daily SBS target was prescribed on 98% of intubated study days and achieved 95% of the time. Arousal assessments were recommended in 4% of titration and weaning phase days. When performed, 61 patients achieved an awake state within 300 minutes (median; interquartile range: 120–480), and 13 patients did not achieve an awake state, requiring sedative infusions to be discontinued or maintained at 50%. An ERT was recommended on 39% of intubated study days, and 80% of successful extubations occurred after passing an ERT.

Outcomes

Primary Outcome—The duration of mechanical ventilation was not statistically significantly different between the two groups (median; interquartile range: intervention: 6.5 days; 4.1–11.2 vs. control: 6.5; 3.7–12.1; P=0.61; Table 2; Figure 2). Adjusting for age group, PRISM III-12 score, and POPC>1 at enrollment, the hazard ratio for being off mechanical ventilation comparing intervention vs. control was 1.01 (95% confidence interval [CI], 0.85–1.19; P=0.95). In this adjusted model, longer mechanical ventilation was associated with higher PRISM III-12 scores (hazard ratio=0.98 for a one-point increase in PRISM III-12 score; 95% CI 0.97–0.99; P<0.001) and higher POPC category (hazard ratio=0.74 comparing POPC>1 to POPC=1; 95% CI 0.65–0.85; P<0.001) but not with age group (hazard ratio=1.08 comparing the middle to the youngest age group; 95% CI 0.94–1.23; P=0.29, and hazard ratio=1.10 comparing the oldest to the youngest age group; 95% CI 0.97–1.24; P=0.13).

Exploratory Secondary Outcomes—There were no group differences in the time to recovery from acute respiratory failure, duration of weaning from mechanical ventilation, or duration of assisted breathing that includes the use of noninvasive ventilation post-endotracheal extubation (Table 2). Fewer patients in the intervention group received neurological testing to evaluate a change in mental status (14% vs. 19%; odds ratio [OR] for receiving testing comparing intervention vs. control=0.72; 95% CI 0.53–0.97; P=0.03; Table 2 and eTable 7). There were no group differences in PICU and hospital lengths of stay or 28- or 90-day inhospital mortality (Table 2 and eTable 8).

There were no significant differences in sedation-related adverse events including inadequate pain management, inadequate sedation management, clinically significant iatrogenic withdrawal, extubation failure, unplanned endotracheal tube/invasive line removal, ventilator-associated pneumonia, catheter-associated bloodstream infection, or new tracheostomy (Table 2 and eTable 9). Two of 11 sedation-related adverse events were statistically significantly different between the groups. First, more patients in the intervention group had post-extubation stridor with chest wall retractions at rest (7% vs. 4%; OR for having stridor comparing intervention vs. control=1.57; 95% CI 1.04–2.37; P=0.03). While more patients experienced stridor, there were no group differences in reintubation of these patients. Second, fewer intervention patients developed stage 2+ immobility-related pressure ulcers (<1% vs. 2%; OR=0.21 for having an ulcer comparing intervention vs. control; 95% CI 0.08–0.53; P=0.001).

Table 3 summarizes the sedation profiles of the two groups. The primary sedation strategy in the intervention group reflected the protocol, that is, the combined use of an opioid and benzodiazepine with morphine and midazolam as the primary agents. The primary sedation strategy in the control group predominantly included three agents: fentanyl as the primary opioid agent, midazolam and, to a lesser extent, lorazepam as the primary benzodiazepine agents, and dexmedetomidine. In addition, more patients in the control group received chloral hydrate (intervention 3% vs. control 15%; OR for receiving chloral hydrate comparing intervention vs. control=0.27; 95% CI 0.10–0.75; P=0.01). There were no differences in the mean daily, peak daily, and cumulative opioid and benzodiazepine doses between the two groups. Intervention patients had fewer days of exposure to opioids (median 9 vs. 10; hazard ratio for being off opioids comparing intervention vs. control=1.27; 95% CI 1.05–1.54; P=0.01).

Measures of wakefulness, pain, and agitation varied by group (Table 3). The percentage of study days in which patients were awake and calm while intubated was higher in the intervention group (median; interquartile range: 86%; 67%-100%; vs. 75%; 50%-100%; P=0.004; Table 3). Patients in the intervention group had a greater percentage of days with any report of a pain score ≥4 (50%; 27%-67% vs. 23%; 0–46%; P<0.001) and any report of agitation with an SBS score +1/+2 (60%; 33–80% vs. 40%; 13–67%; P=0.003), than control patients. There no group differences in the percentage of study days with modal pain score <4 (no pain). Episodic reports of pain or agitation were higher in the intervention group but were effectively managed within 2 hours.

There were no differences in the occurrence of iatrogenic withdrawal by group (Table 3). Reflecting the protocol, fewer intervention patients received methadone (12% vs. 30%; OR for receiving methadone comparing intervention vs. control=0.25; 95% CI 0.14–0.45; P<0.001). Exploring further, across both groups, patients receiving methadone had longer opioid exposure and PICU and hospital lengths of stay (21 days; 14–29 vs. 7; 4–13; P<0.001; 15.3 days; 10.8–23.0 vs. 8.4; 5.3–13.6; P<0.001; and 24 days; 16–38 vs. 13; 8–22; P<0.001, respectively).

Post-hoc analyses were conducted to test for group differences related to the cluster design and secular changes in sedation management over the enrollment period. We explored group differences stratified by age and diagnosis of bronchiolitis and found no differences in duration of mechanical ventilation or sedative exposure (eTables 10 and 11). In both groups, the primary sedation strategy remained the combined use of an opioid and benzodiazepine. The usual care group did not adopt protocolized sedation during the trial. Supplemental use of dexmedetomidine increased each year in both groups and was used more often in the control group (eTable 12).

DISCUSSION

This multicenter, cluster-randomized study of 2449 pediatric patients with acute respiratory failure showed no difference in the duration of mechanical ventilation for patients managed per sedation protocol compared to patients receiving usual care. Exploratory analyses of several secondary outcomes indicated that the sedation protocol was associated with a

difference in patients' sedation experience; patients in the intervention group were able to be safely managed in a more awake and calm state while intubated, receiving fewer days of opioid exposure and sedative classes without an increase in inadequate pain or sedation management or clinically significant iatrogenic withdrawal compared to patients receiving usual care, but experienced more days with reported pain and agitation, suggesting a complex relationship between wakefulness, pain, and agitation.

Targeting a sedation goal of patients who are calm, easily aroused, and readily evaluated is attainable and safe in children ventilated for acute respiratory failure. Prescribing a more awake state during the titration phase of illness decreased sedation exposure and allowed an accelerated weaning schedule from the patient's primary agent that commenced at a lower starting opioid dose. This strategy decreased the need for methadone conversion. The net result was shorter opioid exposure with comparable WAT-1 scores.

Adjustment of sedatives according to trajectory of illness diminished the need for arousal assessments. [8] Few patients were unresponsive or responsive only to noxious stimuli in the titration or weaning phases of the protocol. Patients who are more awake and calm are better able to communicate their level of discomfort, interact meaningfully with their parents and caregivers, and participate in neurological assessments. Episodic pain and agitation were assessed more often in intervention patients and effectively managed in the context of fewer sedative classes and exposure days.

More intervention patients experienced post-extubation stridor and fewer had clinically significant pressure ulcers. Patients who are more awake are better able to move which may produce airway irritation but also allow patients to reposition themselves to avoid pressure-related skin injury. Pressure ulcers are a serious iatrogenic injury adding to the personal and financial burden of critical illness. Shifting treatment approaches away from inactivity may also be helpful given our evolving knowledge on the consequences of critical illness on neuromuscular function in adults. [31,32] Although follow-up studies of more awake adult ICU patients demonstrate no adverse outcomes, [33,34] the relationships between PICU awareness, amnesia, and neurobehavioral outcomes in children are unknown and the subject of future inquiry in a subset of patients.

Intensive care is practiced within an interprofessional team sharing responsibility for patient outcomes. The study protocol focused on how physicians, nurses, pharmacists, and respiratory therapists collaborate to set sedation goals for an individual patient and how sedatives are adjusted to meet a patient's evolving state and readiness for extubation. Unique features of the protocol include disrupting the status quo by using different sedation targets per phase of illness, mandating a decision about sedation adjustment every 8 hours, providing recommendations on when to use secondary agents, and providing a systematic plan to wean high-risk patients. Our data show that the protocol can be implemented to reduce variation in sedation management and that PICU nurses, working within an interprofessional team, can manage sedation in more awake and calm pediatric patients.

There are study limitations, some of which reflect a cluster-randomized design. [13] The intervention group enrolled more patients <2 years of age and more patients with

bronchiolitis – patients who are often very difficult to sedate. Selection bias may have occurred because the trial was unblinded. We minimized this potential bias using explicit enrollment criteria, monitoring sedation practices in both groups, following well-defined outcomes including pre-specified adverse events, and using a statistical analysis plan designed *a priori* that adjusted for age group, PRISM III-12 score, functional health at enrollment, and accounted for PICU as a cluster variable. Post-hoc analyses were conducted to test for group differences related to baseline imbalances, and we found no differences in duration of mechanical ventilation or sedative exposure. Including 31 sites allowed potential bias to be distributed across multiple PICUs with varied baseline practices. This approach allowed a comprehensive assessment of risk that increases the generalizability of study results to a large proportion of critically-ill pediatric patients. The study protocol required personnel time for training and implementation. Whether those implementation costs would be offset by the positive findings on exploratory analyses is not known and warrants further study. Delirium, which is associated with morbidity and mortality in critically-ill adults, [35–37] could not be assessed because pediatric assessment instruments were unavailable at the start of the trial. [38–41] Patients with acute respiratory failure were the focus of this study; whether our results can be extrapolated to other pediatric critically-ill patients requires further study. There were many analyses of secondary outcomes performed, so any positive finding should be considered exploratory. No statistical adjustments were made for multiple comparisons.

Sedation practices could be optimized if the pharmacokinetic and pharmacodynamic profiles of sedatives in critically-ill pediatric patients were better described. [42,43] While *RESTORE* focused on the process of how sedatives are administered, future studies should compare the best sedative agent for varied lengths of critical illness. Outcomes of interest include efficacy as well as an evaluation of the immediate risk-benefit ratio and an evaluation of the long-term impact of sedatives on neurocognitive development [44,45] and post-traumatic stress. [46]

CONCLUSIONS

Among children undergoing mechanical ventilation for acute respiratory failure, the use of a nurse-implemented, goal-directed sedation protocol compared with usual care did not reduce the duration of mechanical ventilation. Exploratory analyses of the secondary outcomes suggest a complex relationship between wakefulness, pain, and agitation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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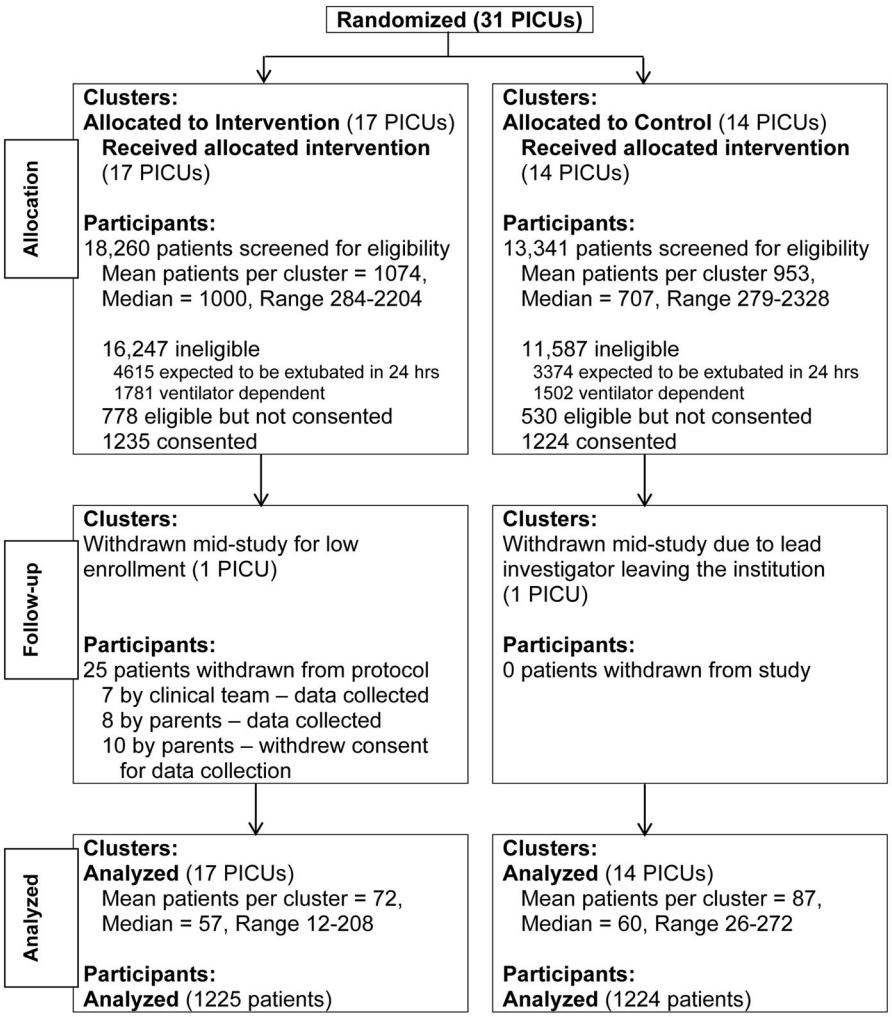

Figure 1.

Flow Diagram of Sites and Study Participants throughout the *RESTORE* Clinical Trial. See also eTable3 for a complete list of reasons patients were ineligible.

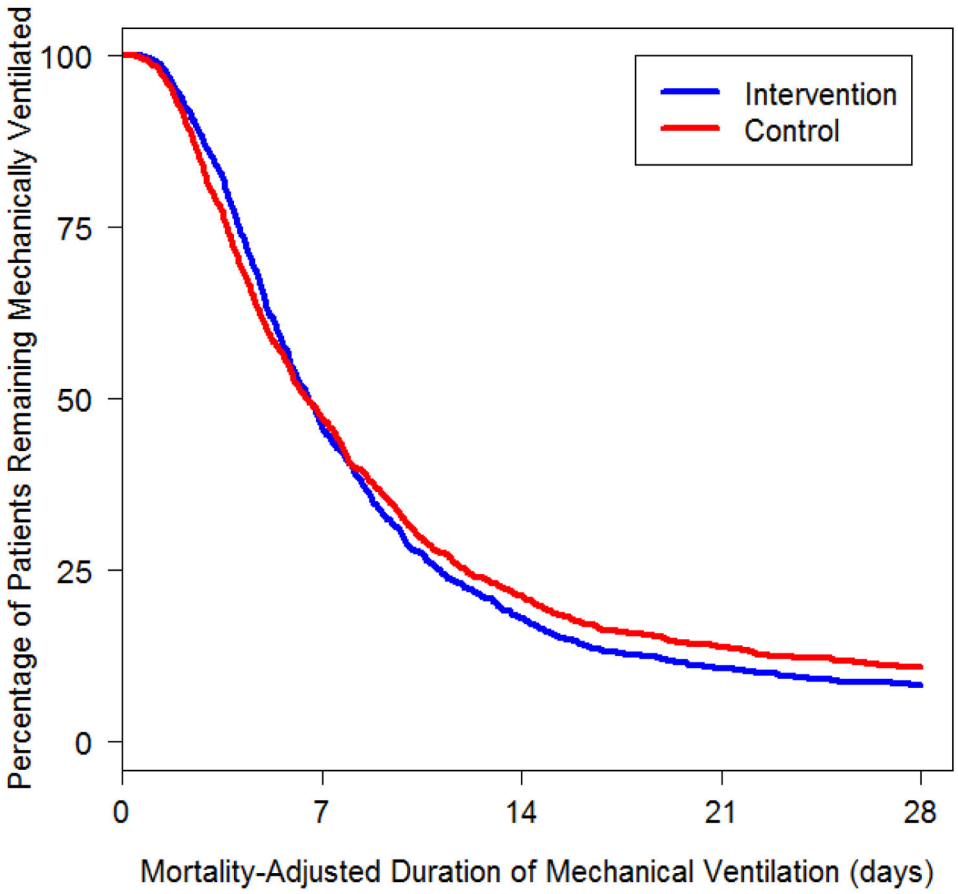

Figure 2.
Kaplan-Meier Plot of the Mortality-Adjusted Duration of Mechanical Ventilation to Day 28, According to Group.

Table 1

Baseline Characteristics of the Study Patients, According to Group.

Variable	Intervention (N=1225)	Control (N=1224)	P Value[a]
Age at PICU admission			
Median (IQR) – years	1.4 (0.3–7.0)	2.6 (0.6–9.2)	0.002
2 weeks to 1.99 years – no. (%)	715 (58)	550 (45)	<0.001
2.00 to 5.99 years	176 (14)	243 (20)	
6.00 to 17.99 years	334 (27)	431 (35)	
Female sex – no. (%)	558 (46)	543 (44)	0.53
Non-Hispanic white – no./total no. (%)	631/1215 (52)	602/1210 (50)	0.81
Baseline PCPC = 1 – no. (%)[b]	942 (77)	923 (75)	0.41
Baseline POPC = 1 – no. (%)[b]	885 (72)	862 (70)	0.51
Able to verbally communicate pain at baseline – no./total no. (%)[c]	398/616 (65)	565/768 (74)	0.21
PRISM III-12 score – median (IQR)	6 (3–11)	8 (5–13.5)	0.005
Percent risk of mortality based on PRISM III-12 score – median (IQR)	2.4 (1.0–9.5)	4.8 (1.7–15.0)	0.01
2 weeks to 1.99 years	1.7 (0.7–4.9)	3.8 (1.3–9.5)	0.003
2.00 to 5.99 years	3.3 (1.2–17.2)	4.8 (1.7–17.0)	0.56
6.00 to 17.99 years	7.7 (1.8–19.6)	7.7 (2.2–26.2)	0.54
Primary diagnosis – no. (%)			<0.001
Pneumonia	394 (32)	433 (35)	
Bronchiolitis	428 (35)	228 (19)	
Acute respiratory failure related to sepsis	145 (12)	212 (17)	
Asthma or reactive airway disease	87 (7)	120 (10)	
Aspiration pneumonia	70 (6)	79 (6)	
Other[d]	101 (8)	152 (12)	
PARDS based on Day 1 OI or OSI – no. (%)[e]			0.83
At risk (OI <4.0 or OSI <5.0)	472 (39)	460 (38)	
Mild (OI 4.0–7.9 or OSI 5.0–7.4)	308 (25)	351 (29)	
Moderate (OI 8.0–16.0 or OSI 7.5–12.3)	279 (23)	254 (21)	
Severe (OI >16.0 or OSI >12.3)	166 (14)	159 (13)	
Neuromuscular blockade for the entire duration of Days 0 to 2 – no. (%)	82 (7)	92 (8)	0.64
Any past medical history – no. (%)			
Prematurity (<36 weeks post-menstrual age)	194 (16)	175 (14)	0.37
Asthma (prescribed bronchodilators or steroids)	146 (12)	210 (17)	0.18
Seizure disorder (prescribed anticonvulsants)	112 (9)	112 (9)	0.76
Neurologic/neuromuscular disorder which places patient at risk for aspiration	105 (9)	96 (8)	0.62
Cancer (current or past diagnosis)	88 (7)	109 (9)	0.31
Known chromosomal abnormality	60 (5)	48 (4)	0.24
Chronic tracheostomy – no. (%)	11 (<1)	11 (<1)	0.74

Variable	Intervention (N=1225)	Control (N=1224)	P Value[a]
Intubated at outside hospital and transferred to participating PICU – no. (%)	334 (27)	306 (25)	0.23

Abbreviations: IQR, interquartile range; OI, oxygenation index; OSI, oxygen saturation index; PARDS, pediatric acute respiratory distress syndrome; [47,48] PCPC, Pediatric Cerebral Performance Category; PICU, pediatric intensive care unit; POPC, Pediatric Overall Performance Category; PRISM III-12, Pediatric Risk of Mortality III score from first 12 hours in the PICU.

[a] P values for the comparison between groups were calculated using linear, cumulative logit, logistic, and multinomial logistic regression accounting for PICU as a cluster variable using generalized estimating equations for log-transformed continuous, ordinal, binary, and nominal variables, respectively.

[b] PCPC and POPC range from 1 to 6, with higher categories indicating greater impairment.

[c] Able to verbally communicate pain at baseline includes only patients aged 16 months and older.

[d] Other primary diagnoses include pulmonary edema, thoracic trauma, pulmonary hemorrhage, laryngotracheobronchitis, acute respiratory failure post bone marrow transplant, acute chest syndrome/sickle cell disease, pertussis, pneumothorax (non-trauma), acute exacerbation lung disease (cystic fibrosis or bronchopulmonary dysplasia), acute respiratory failure related to multiple blood transfusions, pulmonary hypertension (not primary), and other.

[e] Oxygenation index (OI) was calculated as [(FIO2 × mean airway pressure)/PaO2 × 100]. When an arterial blood gas was not available, SpO2 was used to estimate PaO2 in order to calculate oxygen saturation index (OSI) [(FIO2 × mean airway pressure)/SpO2 × 100]. Lower scores reflect better oxygenation.

Table 2

Study Outcomes, According to Group.[a]

Variable	Intervention (N=1225)	Control (N=1224)	P Value[b]
Primary outcome			
Duration of mechanical ventilation – days, median (IQR)	6.5 (4.1–11.2)	6.5 (3.7–12.1)	0.61
Adjusted for age group, PRISM III-12score, and POPC >1 at enrollment[c]			0.95
Not successfully extubated by Day 28 – no. (%)	103 (8)	135 (11)	0.19
Still intubated on Day 28	40 (3)	62 (5)	
Not extubated and died by Day 28	41 (3)	54 (4)	
Still intubated on transfer to another PICU by Day 28	22 (2)	19 (2)	
Secondary outcomes (Non-sedation)			
Time to recovery from acute respiratory failure – days, median (IQR)[d]	2.9 (1.3–6.0)	2.4 (1.1–5.7)	0.91
Duration of weaning from mechanical ventilation – days, median (IQR)[e]	2.3 (1.1–4.3)	2.4 (1.2–5.1)	0.33
Duration of assisted breathing – days, median (IQR)[f]	8.0 (4.8–14.1)	7.7 (4.1–14.8)	0.97
Neurological testing – no. (%)	175 (14)	230 (19)	0.03
PICU length of stay – days, median (IQR)[g]	9.6 (6.2–15.6)	9.6 (5.7–16.6)	0.61
Hospital length of stay – days, median (IQR)[g]	14 (9–24)	16 (9–29)	0.20
In-hospital mortality – no. (%)			
28-Day in-hospital mortality	47 (4)	63 (5)	0.22
90-Day in-hospital mortality	67 (5)	88 (7)	0.18
Sedation-related adverse events [18]			
Inadequate pain management – no. (%)[h]	195 (16)	174 (14)	0.65
Inadequate sedation management – no. (%)[i]	301 (25)	246 (20)	0.93
Clinically significant iatrogenic withdrawal – no. (%)[j]	149 (12)	114 (9)	0.80
Extubation failure (reintubation within 24hours) – no. (%)	97 (8)	104 (9)	0.56
Post-extubation stridor with chest-wall retractions at rest – no. (%)	88 (7)	55 (4)	0.03
Unplanned endotracheal tube extubation – no. of events/100 ventilator days	0.41	0.53	0.76
Unplanned removal of any invasive tube – no. of events/100 device days	0.16	0.12	0.22
Ventilator-associated pneumonia – no. of events/1000 ventilator days	0.53	0.77	0.38
Catheter-associated bloodstream infection – no. of events/1000 central line days	0.86	0.77	0.64
Immobility-related stage 2+ pressure ulcers – no. (%)	5 (<1)	19 (2)	0.001
New tracheostomy – no. (%)[k]	16 (1)	33 (3)	0.12

Abbreviations: IQR, interquartile range; PICU, pediatric intensive care unit; POPC, Pediatric Overall Performance Category; PRISM III-12, Pediatric Risk of Mortality III score from first 12 hours in the PICU.

[a] See also eTable 4 for outcomes definitions.

[b] P values for the comparison between groups were calculated using proportional hazards, logistic, and Poisson regression accounting for PICU as a cluster variable using generalized estimating equations for time-to-event, binary, and rate variables, respectively, except where otherwise noted under the primary outcome.

[c] After adjusting for age group, PRISM III-12 score, and POPC >1 at enrollment, the intraclass correlation coefficient based on the deviance residuals was 0.046.

[d] Time to recovery from acute respiratory failure excludes 120 nonsurvivors who did not meet criteria prior to death. For the 213 survivors who never met criteria, the duration of recovery was set equal to the duration of mechanical ventilation if the patient was successfully extubated or to 28 days if the patient was still intubated on Day 28 or transferred to another ICU still intubated.

[e] Duration of weaning from mechanical ventilation excludes 144 nonsurvivors who were not extubated for >24 hours prior to death. Also excludes 213 survivors who never met criteria and 73 survivors still intubated on Day 28.

[f] Duration of assisted breathing continued until the first time pressure support was <5 cm H2O (continuous or bi-level) for at least 24 hours. Patients were assigned 28 days if they remained on pressure support ≥5 cm H2O or were transferred or died prior to Day 28 without remaining off pressure support ≥5 cm for >24 hours.

[g] PICU and hospital length of stay exclude all non-survivors. Patients still in the PICU or hospital on Day 90 were censored at Day 90.

[h] Inadequate pain management was defined as a pain score >4 (or pain assumed present if receiving neuromuscular blockade) for 2 consecutive hours, not related to a planned extubation attempt.

[i] Inadequate sedation management was defined as agitation (SBS >0, or agitation assumed present if receiving neuromuscular blockade) for 2 consecutive hours, not related to a planned extubation attempt.

[j] Clinically significant iatrogenic withdrawal was defined as rescue therapy (an opioid or benzodiazepine bolus or an increase in opioid or benzodiazepine infusion) to manage an increase in withdrawal symptoms for patients weaning from ≥5 days of opioids.

[k] Excludes 22 patients admitted with tracheostomies.

Table 3

Sedation Profiles, According to Group.[a]

Variable	Intervention (N=1225)	Control (N=1224)	P Value[b]
Sedatives administered			
Primary opioid agent – no. (%)[c]			
Morphine	782 (64)	210 (17)	<0.001[d]
Fentanyl	431 (35)	989 (81)	
Hydromorphone (non-protocol sedative)	2 (<1)	10 (<1)	
Remifentanil (non-protocol sedative)	1 (<1)	0	
None	9 (<1)	15 (1)	
Opioid exposure – mg/kg, median (IQR)			
Mean daily dose	1.3 (0.7–2.6)	1.7 (0.8–2.9)	0.13
Peak daily dose	3.3 (1.6–6.1)	4.0 (2.0–7.0)	0.16
Cumulative dose	13.7 (5.3–38.3)	17.7 (5.3–52.9)	0.10
Exposure days – median (IQR)	9 (5–15)	10 (4–21)	0.01
Primary benzodiazepine agent – no. (%)[c]			
Midazolam	1087 (89)	1009 (82)	0.02[e]
Lorazepam	128 (10)	206 (17)	
None	10 (<1)	9 (<1)	
Benzodiazepine exposure – mg/kg, median (IQR)			
Mean daily dose	1.3 (0.6–2.7)	1.3 (0.6–2.5)	0.22
Peak daily dose	2.9 (1.5–6.0)	3.2 (1.5–6.7)	0.77
Cumulative dose	14.0 (5.1–41.5)	13.6 (4.3–42.4)	0.54
Any secondary sedatives – no. (%)			
Dexmedetomidine	287 (23)	596 (49)	<0.001
Propofol	171 (14)	137 (11)	0.87
Barbiturates	142 (12)	226 (18)	0.37
Ketamine	261 (21)	368 (30)	0.058
Clonidine	149 (12)	163 (13)	0.87
Methadone	148 (12)	368 (30)	<0.001
Chloral hydrate (non-protocol sedative)	34 (3)	181 (15)	0.01
Number of different sedative classes received – median (IQR)[f]	2 (2–3)	3 (2–4)	<0.001
0 – no. (%)	1 (<1)	2 (<1)	
1	9 (<1)	10 (<1)	
2	620 (51)	350 (29)	
3	347 (28)	416 (34)	
4	167 (14)	264 (22)	
5–7	81 (7)	182 (15)	

Variable	Intervention (N=1225)	Control (N=1224)	P Value[b]
Hypnotic medications – no. (%)	82 (7)	81 (7)	0.57
Anti-delirium medications – no. (%)	20 (2)	26 (2)	0.33
Neuromuscular blockade to manage agitation – no. (%)	290 (24)	326 (27)	0.66
Measures of wakefulness, pain, and agitation			
Percentage of study days awake and calm (modal SBS score -1 or 0) – median (IQR)	86 (67–100)	75 (50–100)	0.004
Days to first awake/calm – median (IQR)[g]	2 (1–4)	2 (1–4)	0.09
Percentage of study days with modal pain score <4 – median (IQR)	100 (100–100)	100 (100–100)	0.84
Percentage of study days with an episode of pain (highest pain score ≥4)	50 (27–67)	23 (0–46)	<0.001
Percentage of study days with an episode of agitation (highest SBS score +1 or +2)	60 (33–80)	40 (13–67)	0.003
Occurrence of iatrogenic withdrawal[h]			
Iatrogenic withdrawal syndrome (WAT-1score ever ≥3) – no. (%)	450 (68)	336 (68)	0.80
Peak WAT-1 score – median (IQR)	4 (2–5)	4 (2–6)	0.90
Percentage of study days with WAT-1score ≥3 – median (IQR)	25 (0–50)	25 (0–50)	0.83

Abbreviations: IQR, interquartile range; SBS, State Behavioral Scale; WAT-1, Withdrawal Assessment Tool – Version 1.

[a] See also eTable 4 for outcomes definitions.

[b] P values for the comparison between groups were calculated using logistic, linear, and proportional hazards regression accounting for PICU as a cluster variable using generalized estimating equations for binary variables, log-transformed continuous variables (except percentage of study days variables), and time-to-event variables, respectively.

[c] Primary opioid agent was defined as the opioid administered via continuous infusion. If no opioid or more than one opioid was administered via continuous infusion, primary opioid agent was defined as the opioid administered on the highest percentage of study days. If morphine and fentanyl were administered on the same number of days, primary opioid agent was assigned as the opioid contributing the highest morphine equivalents. Primary benzodiazepine agent was defined similarly. If midazolam and lorazepam were administered on the same number of days, primary benzodiazepine agent was assigned as the benzodiazepine contributing the highest midazolam equivalents.

[d] This P value compares primary agent morphine vs. fentanyl between groups. Fentanyl was recommended in patients with profound hypotension, unremitting reactive airways disease, or intolerance to morphine.

[e] This P value compares primary agent midazolam vs. lorazepam between groups. Enteral lorazepam was recommended if intravenous access was a problem or if the patient was tolerating enteral feedings.

[f] Different sedative classes include opioids, benzodiazepines, alpha2-adrenergic agonists, propofol, barbiturates, ketamine, and chloral hydrate.

[g] See also eFigure 1.

[h] WAT-1 scores range from 0–12; higher WAT-1 scores indicate more withdrawal symptoms; WAT-1 scores ≥3 are associated with clinically significant withdrawal symptoms. Peak WAT-1 scores and percentage of study days with WAT-1 score ≥3 reported were calculated for 1157 survivors who completed weaning from ≥5 days of opioids and had at least one WAT-1 assessment (660 intervention and 497 control patients).