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Contextualizing iatrogenic withdrawal syndrome and delirium in pediatric critical care

Kaitlin M. Best, PhD, RN,

Cardiac Intensive Care Unit, The Children's Hospital of Philadelphia, Philadelphia, PA 19104

David Wypij, PhD,

Department of Cardiology, Boston Children's Hospital, Boston, MA 02115. Department of Pediatrics, Harvard Medical School, Boston, MA 02115. Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA 02115

Lisa A. Asaro, MS, and

Department of Cardiology, Boston Children's Hospital, Boston, MA 02115

Martha A. Q. Curley, PhD, RN, FAAN

Ellen and Robert Kapito Professor of Nursing Science, School of Nursing. Department of Anesthesia and Critical Care Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104

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We thank Drs. Traube and Silver for their thought-provoking letter, in which they speculate whether some of the *RESTORE* patients who experienced iatrogenic withdrawal syndrome (IWS) “actually had delirium rather than, or in addition to, withdrawal” (1). As noted in the original publication, we did not systematically screen for delirium in the *RESTORE* clinical trial because pediatric delirium assessment instruments were unavailable at the trial's start in 2009 (2).

After probing the *RESTORE* dataset, we identified 2% of patients (49/2449) who received antidelirium medications (N=46) and/or experienced hallucinations or clinician-reported delirium (N=9; 3 did not receive antidelirium medications), adverse events that were not pre-specified. Most patients (82%) with “presumed delirium” were in our oldest age group (6–17 years) and were cognitively appropriate for age (82%). The onset of the presumed delirium

Corresponding Author: Martha A. Q. Curley, PhD, RN, FAAN, 418 Curie Blvd - #425, Philadelphia, PA 19104, curley@nursing.upenn.edu, Office: (215) 573 9449.

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was on study day 5 (median; interquartile range, 2–12). Only approximately a third (N=18) were ever at-risk for IWS. Among these 18 patients, 5 experienced presumed delirium only after the start of weaning. These 5 patients were assessed for IWS using the WAT-1 (3) for 3–12 days and exhibited a variety of withdrawal symptoms. We have no way to retrospectively identify hypoactive delirium in the *RESTORE* dataset and believe we are underreporting hyperactive delirium, but most of the presumed delirium we captured did not overlap with IWS.

Interpreting clinical symptoms in the context of the patient's trajectory of illness is crucial when differentiating IWS from delirium. Organ dysfunction, including the brain, is common in critically ill patients. In addition, shortly after ICU admission, most patients experience circadian disruption and other exposures that influence delirium risk. The primary challenges during the acute phase of illness are to manage pain and agitation while stabilizing the patient. Ensuring patient comfort remains a priority throughout the course of illness and may require upward titration of both analgesics and sedative medications as tolerance develops. The greatest potential for overlap between IWS and delirium exists during the weaning phase, when the gradual cessation of analgesic and sedative medications coupled with the stress of a protracted PICU stay may trigger one or both conditions.

Our work represents a step towards identifying risk factors for IWS that could drive further prevention efforts. The WAT-1 was developed in patients known to be weaning from opioids and/or benzodiazepines (3). Our subspecialty now has several standardized assessment tools that will allow for prospective monitoring of delirium (4–6). Going forward, we recommend that future studies of IWS in patients weaning from sedation include delirium monitoring throughout the patient's course of illness to allow prospective study of factors associated with both phenomena. Such research should account for variation in analgesia and sedation practices, patient response to medications, the PICU environment, and the patient's trajectory of illness. We appreciate the opportunity to address the complex interplay between IWS and delirium in the PICU, which we hope will form the basis for a robust program of research that will improve care for all critically ill children.

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