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LESS IS MORE IN INTENSIVE CARE

Scheduled intravenous opioids

Cathrine McKenzie[1,2,3], Yoanna Skrobik[4,5] and John W. Devlin[6,7*]

Maintaining comfort and analgesia is fundamental to providing adequate care in intensive care unit (ICU) patients. Pain assessment and its control remain the highest priorities and concerns among survivors of critical illness and their loved ones [1]. A single, dose-appropriate, intravenous (IV) opioid bolus should be considered for patients with severe pain or before a painful procedure [1, 2]. Scheduled IV opioids (i.e., scheduled intermittent boluses and/or continuous infusions) are, and have been for decades, the mainstay of ICU analgesia. IV opioids were recommended as the first-choice analgesic for non-neuropathic pain in 2013 practice guidelines [3]. Their use remains prevalent both during and after ICU stay. A current 29-country ICU point-prevalence study reports 87% of patients received scheduled IV opioids the previous day [4]. In another contemporaneous study in the United Kingdom (UK), 87.5% of ICU patients received continuous opioid infusions [5]. Among opioid-naive Swedish ICU survivors, 5% took opioids chronically a year later [6].

Pharmacologically, opioids in pain management have important limitations [7, 8]. These include highly variable individual and gender-based responses, limited pain modulation for common ICU pain domains, and rapid tolerance, particularly with ultra-short-acting agents like remifentanil and alfentanil, whose mu-receptor affinity is the highest [9]. Mechanistic similarities have been proposed for opioid tolerance, hyperalgesia, and the development of chronic pain syndromes [7, 9]. The relationship between opioid exposure and pain reduction is not well-established [2]; no evidence supports ICU opioid effectiveness [7]. IV opioids have complex pharmacokinetic and pharmacogenomic properties, often leading to unpredictable response and clearance in critically ill adults [8, 10]. Biologic opioid dependence is established in adults after 3–5 days and in children administered continuous opioid infusions after 72 h [7–9]. After long-term opioid exposure, pain-associated discomfort may be indistinguishable from iatrogenic withdrawal syndrome (IWS) symptoms [7]. Although a validated IWS assessment tool does not exist for nonverbal critically ill adults, one in every eight medical ICU patients receiving IV opioid infusions for > 24 h had clinical signs of IWS when assessed using the clinical opioid withdrawal scale (COWS) [11].

Opioid use in the ICU raises important safety concerns [7, 8]. Constipation, common with opioid use, causes nausea and vomiting, increased abdominal distension and pressure, and reduced capacity for enteral feeding, in addition to esophageal motility abnormalities [12]. Stool softeners and osmotic laxatives are often ineffective [8]. The histamine release associated with natural opioids (e.g., morphine) can provoke bronchospasm and hypotension [8]. Muscle rigidity is common with fentanyl; this, in turn, may compromise early exercise and mobility goals [1, 8]. Opioids increase delirium risk in a dose-related fashion independently from pain [13]. As a drug class, opioids disrupt sleep, are immunosuppressive, trigger hormonal abnormalities like adrenal axis and pituitary hormone pathway suppression and hypogonadism in both sexes, alter bone metabolism and may worsen despondency through their kappa and delta receptor effects [1, 7, 8].

The controlled evidence supporting the use of analgesia-based sedation (i.e., opioid infusions to manage sedation in lieu of anxiolytic medications) is older, flawed, heterogeneous, and not applicable to current pain and sedation goals for most mechanically

*Correspondence: j.devlin@neu.edu
[6] School of Pharmacy and Pharmaceutical Sciences, Bouve College of Health Sciences, Northeastern University, Boston, MA, USA
Full author information is available at the end of the article

Table 1 Strategies to reduce scheduled IV opioid use in the ICU

Symptom	Non-pharmacologic	Pharmacologic
Pain (non-neuropathic)	Use an assessment-based pain management protocol In patients unable to self-report, and where ventilator discomfort is suspected to be a manifestation of pain, validate that this discomfort produces similar behaviors to that observed with nociceptive stimuli using criterion from validated behavioral tools (e.g., Behavioral Pain Scale). Other behavioral pain 'scoring' items (e.g., forearm tension as evaluated with the Clinical Pain Observational Tool) may be more psychometrically valid for corroborating pain symptoms than ventilator compliance	
	Multimodal use of cold therapy, positioning, music, massage, relaxation techniques, empathy, and distraction	Multimodal use of regional nerve block(s), paracetamol, low-dose ketamine
Pain (neuropathic)	Multimodal use of neurostimulation, cold therapy, massage, relaxation techniques, empathy, and distraction	Pregabalin or gabapentin
Agitation	Identify and reduce underlying causes including nausea, full bladder, delirium, disrupted sleep, substance withdrawal. Increase exercise and mobility [14]	If agitation persists despite assessment and non-pharmacologic intervention(s); consider short-term (< 24 h) trial of low-dose dexmedetomidine or propofol infusion. Consider intermittent benzodiazepines for agitation related to substance withdrawal
Anxiety	Communication, family presence, psychologic assessment, music, remove restraints	Continuation of home anxiolytics, initiation of short-term intermittent anxiolytics
Ventilator asynchrony	Identify which ventilator asynchrony is most likely present (e.g., triggering delay, ineffective effort, auto-triggering, double-triggering, reverse-triggering, flow, cycling) and adjust the ventilator settings accordingly. Incorporate R (respiratory drive management) in the ABCDEF bundle to avoid overuse of opioids and sedatives [17]	Short-term propofol or intermittent midazolam realizing, like opioids, each may worsen ventilator asynchronies

ventilated adults [1]. Current evidence supports focusing on light (or even no) sedation, and the managing agitation primarily through symptom reduction and non-pharmacological approaches [1, 14, 15]. IV opioids exacerbate ventilator dyssynchrony (rather than treat it) [16]. Ventilator adjustment and other strategies to reduce respiratory drive are preferred over IV opioid infusions in ICU populations at risk for asynchrony [17].

So what can we do as a community to reduce scheduled IV opioids in our ICUs?

Routine pain assessment using validated methods is mandated by guidelines [1, 3] and regulatory bodies. However, bedside clinicians often rely on their opinions about what their patients' pain should be rather than patients' self-report, are unlikely to adopt the results of behavioral pain assessments in non-verbal patients, and use clinical measures (e.g., vital signs) that do not correlate with pain to characterize it [1]. Opioids are often not adjusted to pain scores [7]. Use of an assessment-based, pain management protocol reduced opioid consumption by 80% at one center [15]. Guideline recommendations support non-opioid analgesics, such as regional nerve blocks, paracetamol, gabapentinoids, and low-dose ketamine, as well as non-pharmacologic strategies like cold-therapy to reduce opioid exposure and/or improve pain in ICU subgroups [1]. Some of these analgesics rely on a functional gut to be administered (e.g., gabapentinoids). Others are best-suited for severe pain (e.g., ketamine). While the quality of evidence to support ICU multimodal analgesic use remains relatively low, it remains stronger than the evidence to support routine scheduled IV opioid use [1, 3, 7].

Admission orders for ICU patients should limit IV opioids to pain assessment-driven clinical parameters above a determined threshold, after other, and safer, therapeutic options (e.g., multimodal analgesic strategies including regional nerve blocks, scheduled paracetamol and non-pharmacological therapies, including empathy and distraction) have failed. The admitting intensivist, senior team, nurse, and clinical pharmacist should consider: "does this individual patient's management warrant IV opioid by continuous infusion, or indeed any scheduled IV opioid?" daily. Pain assessment-driven opioid administration reduces opioid use and improves pain control in medical and surgical patients [1, 7]. In addition to a philosophy of dynamic, as needed, ICU opioid prescribing, analgesic prescriptions should be reviewed daily. Deprescribing efforts focused on transitioning to scheduled multi-modal, non-opioid analgesic and restricting opioid use to an 'as needed' basis only should be adopted. Incentives to monitor and reduce scheduled IV opioids by beside clinicians are an important, much-needed quality improvement metric.

Additionally, the language within the critical care community, and vis-à-vis our patients and their families, surrounding scheduled IV opioid use, must change. All too

frequently, we substitute the term 'sedation' for the opioids we administer and downplay the ICU and post-ICU risks of the opioids we choose to prescribe. Discussing the risks and benefits of scheduled IV opioids must occur with patients and their families. Finally, the ICU community has been slow to call for research funding organizations and the pharmaceutical industry to boost the development of analgesic alternatives to opioids for our patients who are in pain.

Strategies that ICU clinicians can employ to reduce scheduled IV opioid use are highlighted in Table 1.

Author details
[1] National Institute of Health and Social Care Research (NIHR) Biomedical Research Centre, School of Medicine, Perioperative and Critical Care Theme and NIHR Applied Research Collaborative (ARC), University of Southampton, Wessex, Southampton, UK. [2] Pharmacy and Critical Care, University Hospital, Southampton NHS Foundation Trust, Southampton, UK. [3] Institute of Pharmaceutical Sciences, School of Cancer and Pharmacy, King's College London, London, UK. [4] Department of Medicine, McGill University, Montreal, QC, Canada. [5] Department of Medicine, Cambridge University, Cambridge, UK. [6] School of Pharmacy and Pharmaceutical Sciences, Bouve College of Health Sciences, Northeastern University, Boston, MA, USA. [7] Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, MA, USA.

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