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# Next steps in ICU pain research

Kathleen Puntillo<sup>1\*</sup> , Céline Gélinas<sup>2</sup> and Gerald Chanques<sup>3,4</sup>

## Introduction

Assessment and management of pain in intensive care unit (ICU) patients have profited from 25 years of research. Many advances have been made to identify when patient pain is present and to test interventions that will improve patient comfort. This article highlights ICU pain research advances, identifies gaps that need attention, and suggests “next steps” in pain research.

## Next steps in ICU pain assessment research

Routine monitoring of pain in all adult ICU patients using validated assessment tools that are adapted to the patient’s ability to communicate is an essential practice requirement [1]. While self-report scales have been compared and validated in ICU patient populations [2], behavioral scales are necessary for patients unable to self-report. The Behavioral Pain Scale (BPS) and the Critical-Care Pain Observation Tool (CPOT) have shown the most robust psychometric properties for use in many ICU patients [3], including delirious patients [4, 5]. Yet, their validity remains to be established in patients with burns, cognitive deficits, brain injuries, and in unconscious or heavily sedated patients [6]. The newly developed Behavior Pain Assessment Tool (BPAT), which is a checklist of the presence or absence of eight behaviors, has been shown to be valid in an international procedural pain study [7]. Further validation of the BPAT, BPS, and CPOT is necessary so that ICU clinicians have alternative pain behavior instruments that they can use with confidence in more patient groups.

Although conducting pain assessments has shown positive effects on ICU pain management and patients’ outcomes [e.g., ICU length of stay and mechanical ventilation (MV) duration], observational pre-experimental designs were used in previous studies. A higher level of evidence (i.e., experimental design) is needed to draw firm conclusions. See Table 1 for suggestions for future pain assessment research.

Other relevant avenues in ICU pain assessment research include studies of physiological measures of pain (excluding vital signs that have been shown to be invalid pain indicators) [1]. Pupil dilation reflex, in association with behavioral pain scores, has shown promising results in predicting procedural pain [8]. The nociceptive level (NoL) index incorporates multiple physiologic parameters into a single index for estimating pain level and was demonstrated to be valid in anesthesia [9]. Its validation in ICU patients to predict pain is an important next step. Finally, a future research consideration is use of families to identify patient pain behaviors while acknowledging culturally different approaches to, yet an increased focus on, ICU patient-family engagement [6] (also see <http://www.iculiberation.org>).

Each pain assessment method discussed above has a similar goal: to identify the presence of, and response to, pain. Yet, each method attends to various dimensions of pain: the sensory and cognitive dimensions of pain as per self-report scales; the behavioral dimension as per behavioral scales; and the stress regulation dimension as per physiological response parameters [10]. Clinicians can choose pain measure(s) and researchers can approach future studies according to a hierarchical structure of pain assessment: self-report methods when possible and then observation and validation of pain behaviors [11] (see Table 1). Future research can also expand our current knowledge of positive clinical processes and patient outcomes that result from standardized use of valid self-report and pain behavior instruments. Outcomes include decreased use of sedatives and analgesics, decreased incidence of pain, and decreased MV [6].

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**Take-home message:** Knowledge about pain in ICU patients has advanced considerably over the past several years. Analysis of the limitations and gaps in this prior research provides direction for research that could lead to improvements in the comfort of ICU patients.

**Table 1 Pain research in intensive care units: future considerations**

Research target	Specific focus	Research design
Pain assessment		
Relationship between self-report and behavioral pain measures	Comparison among mild, moderate, and severe pain cutoff points on self-report and behavioral pain measures	Descriptive psychometric studies
Validation of BPS and/or CPOT in specific ICU patient populations	Patients with burns, cognitive deficits, brain injuries; unconscious or heavily sedated patients (e.g., with Glasgow Coma Scale score of 4–8 or Richmond Agitation Sedation Scale score of –3 to –4)	Comparative descriptive research
Revision of BPAT items and BPAT validation according to recommendations [7]	Evaluation of procedural pain in communicative patients receiving a standardized pre-procedural dose of analgesia; use of revised BPAT and self-report scale such as numeric rating scale	Comparative descriptive, psychometric research
Feasibility of BPAT use	ICU nurse evaluation of ease of use of revised BPAT in practice	Descriptive research
ICU staff and family members' perception of role of the family in the ICU pain assessment process	Cultural differences among countries regarding family engagement in the ICU, with a focus on patient pain assessment	Descriptive research
Families as proxy reporters of patient pain	Comparison of behavioral pain tool notations between ICU patient's nurse and family member	Comparative, descriptive research
Validation of physiologic measures of pain, excluding vital sign measurement and including pupillometry and/or the NoL index	Pupillary reflex and NoL in ICU patients pre-procedural and when undergoing a specific procedure such as turning or chest tube removal under different levels of analgesia	Methodological research; experimental research
Pain management		
Characterization of opioid withdrawal and opioid-induced hyperalgesia in patients receiving opioids	Patients receiving continuous infusions of opioids for at least 3 days	Descriptive research
Side-by-side comparison of analgesics	Opioids vs non-opioids vs both opioids and non-opioids	Prospective, comparative research
Impact of a multimodal analgesia regime on ICU patient outcomes	Multimodal analgesia. Patient ICU-related outcomes such as duration of MV, LOS, infections, ileus, delirium and post-ICU outcomes such as post-traumatic stress disorder, chronic pain syndromes, and opioid dependence	Longitudinal descriptive research; experimental research
Pain assessment and management		
Effects of integrating use of appropriate pain assessment methods (i.e., patient self-report and/or behavioral scales) into the pain management decision-making process	Assessment of sedative and analgesics use, agitation and delirium, duration of mechanical ventilation, LOS	Randomized controlled trials to test outcomes such as effects of integrated pain assessment and management protocols on patients' pain experiences and clinical outcomes
Effectiveness of an analgosedation protocol in decreasing pain and agitation in select groups of ICU patients	Assessments of pain and agitation using behavioral observation scales. Assessments by both patient caregivers and investigators blinded to medications administered	Use of a cluster design to avoid cross-contamination practices between groups

NoL nociceptive level, MV mechanical ventilation, LOS length of stay

**Next steps in ICU pain management research**

Optimizing analgesia can be advanced by considering two separate but related concepts: analgosedation and multimodal analgesia. Analgosedation prioritizes use of analgesics before sedatives (“analgesia first”). The purpose is to decrease sedative doses and their potential negative consequences [delirium, increased MV duration, length of stay (LOS), and mortality] [12] while improving patient comfort.

In performing “analgesia first,” opioids are often the first-line because they are the most effective in abolishing nociceptive pain and are easy to administer [1]. However, the “ventilatory inhibitory” effect of opioids can lead to prolonged MV weaning and may result in opioid

withdrawal syndrome or opioid-induced hyperalgesia, especially when remifentanyl is used because of its very short elimination time [1].

Unfortunately, many analgosedation protocols omit use of valid pain assessment tools, a key component of evaluating “analgesia-first” interventions. While ethics of comparing “sedatives first” versus “analgesics first” when patient pain is a concern, before-and-after studies could compare analgesics versus sedatives regarding patient pain and agitation while using valid scales [13]. Subsequent randomized controlled trials (RCT) could compare ICUs that implement an analgesia-first protocol to ICUs that use sedatives first. A well-designed RCT with investigator blinding could provide evidence of better outcomes

from an analgesia-first approach and confirm the importance of systematically assessing pain and sedation with valid instruments. Results could enhance dissemination and application of pragmatic research to practice. Table 1 presents pain management research recommendations.

While improving pain management for ICU patients, it is necessary to minimize side effects of analgesics. A “multimodal analgesia” approach has long been used outside of ICUs for postoperative analgesia [14] to minimize opioids and their related side-effects: hallucinations, ileus, immunosuppression. These same complications are relevant in ICU because they are frequent baseline risks for many ICU patients and are associated with negative outcomes. With multimodal analgesia, use of non-opioid analgesics such as acetaminophen, nefopam, ketamine, and dexmedetomidine may lower opioid requirements [15]. Non-opioids can also be combined with regional anesthetics and/or non-pharmacological techniques such as relaxation and music therapy. RCTs could assess the impact of a multimodal analgesia protocol administered preemptively, with side-by-side comparisons of opioids, non-opioids, and their combined use while potentially decreasing opioid overuse and toxicities. Outcomes measurements should be comprehensive, as seen in early postoperative rehabilitation programs [14].

In conclusion, ICU pain research is past its childhood phase. In this next, “mature” phase, ICU researchers can pursue new or “nuanced” pain assessment and management methods. New avenues for ICU pain researchers include the pursuit of effective physiological measures such as pupillometry, novel technologies which simultaneously incorporate multiple physiologic parameters, the effects of prolonged drug exposure, and analgesic dosing according to gender, weight, and ethnicity. “Nuanced” methods can employ complex research designs to demonstrate effective pharmacologic and/or complementary analgesic interventions that integrate pain assessment and management processes into protocols and daily practices of ICU care.

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**Compliance with ethical standards**

**Conflicts of interest**

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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