Chapter 2
Assessment of Pain in the Intensive Care Unit

Athir H. Morad and Robert D. Stevens

Pain in the Intensive Care Unit

The pain response is one of the most important phylogenic adaptations in evolution [1]. The extreme rarity of a congenital insensitivity to pain (e.g. autosomal recessive SCN9A gene mutation) underscores the importance of an intact pain response for maintaining tissue integrity and survival of the organism from early infancy [2]. Critically ill patients are exposed to a wide range of painful stimuli—including primary disease, organ failure, surgery, instrumentation and devices, and confinement to bed. It follows that effective pain management is a fundamental priority in intensive care medicine. However, the intensive care unit (ICU) presents many challenges to effective assessment and treatment of pain. Patients may have impaired capacity to communicate pain due to intubation, sedation, induced paralysis, or brain dysfunction. Overmedication with analgesics can mask symptoms of life-threatening processes, while insufficient analgesia can overwhelm patients and distract from the diagnosis of concurrent and potentially significant

A. H. Morad (✉)
Departments of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA
e-mail: morada@jhmi.edu

R. D. Stevens
Departments of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Departments of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Departments of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Departments of Radiology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
e-mail: rstevens@jhmi.edu

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illness or injuries. Additionally, growing concerns over opioid safety and the harms of addiction, discussed throughout this book, underscore the need for prudence in prescribing opioids. The cornerstone to effective management of pain is to measure it. In this chapter, we review different instruments used for the assessment of pain in the ICU.

Neuroanatomy of Pain

A comprehensive account of spinal cord dorsal horn integration and modulation of nociceptive signals is beyond the scope of this chapter. The mechanisms underlying reflex withdrawal from a painful stimulus have been elucidated in some detail. When peripheral nociceptors are activated by a noxious stimulus, neural signals reach the dorsal ganglia adjacent to the spinal column and enter the dorsal horns of the spinal cord. Interneurons transmit the signals to motor neurons within the anterior horn of the spinal cord to trigger an immediate, reflexive, motor response to deflect from the nociceptive source (Fig. 2.1). The spinal cord segment network also projects to cortical pain centers via the spinothalamic tract which conducts signals from the dorsal horn to the thalamus and then to the cortex where the perceptual and emotional responses to pain are generated. The cerebral cortex in turn modulates pain signaling in the spinal cord via descending pathways (Fig. 2.2) [3]. In addition to nociception from somatic structures throughout the periphery, visceral afferent stimuli caused by stretching, spasm, ischemia, or inflammation of pelvic, abdominal, thoracic, and cervico-facial organs can also be transmitted via the dorsal horn of the spinal cord to elicit a pain response.

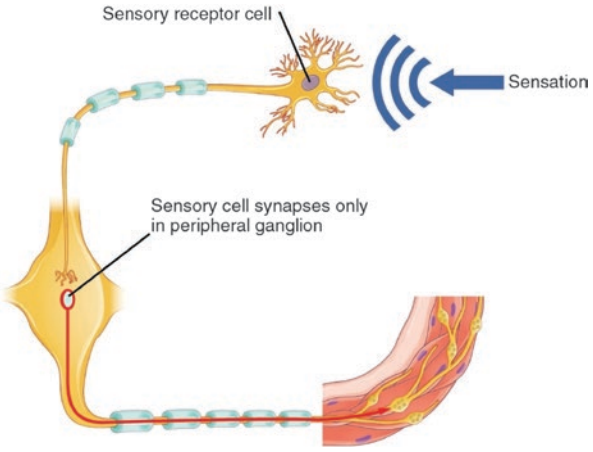

Fig. 2.1 Pain Reflex Arc (Modified Source: "1507 Short and Long Reflexes. jpg," by OpenStax College, https://upload.wikimedia.org/wikipedia/commons/6/68/1507_Short_and_Long_Reflexes.jpg, Licensed under the Creative Commons Attribution 3.0, https://creativecommons.org/licenses/by/3.0/deed.en)

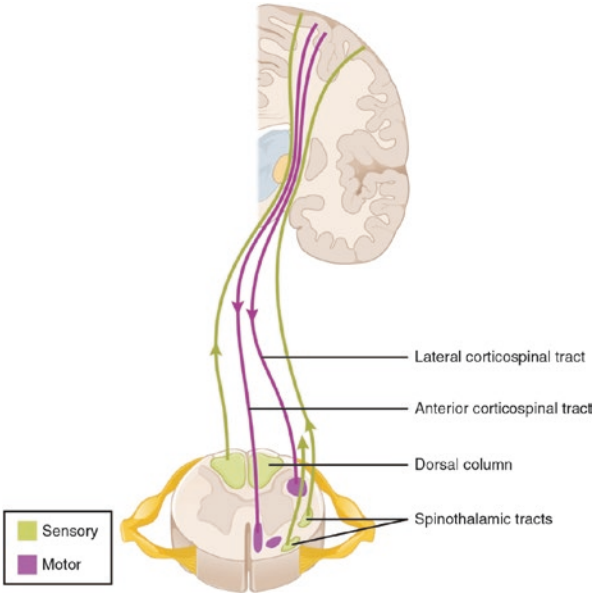

Fig. 2.2 Spinothalamic tract. (Source: 1615 Locations Sinal Fiber Tracts.jpg by Open Stax College. https://upload.wikimedia.org/wikipedia/commons/4/40/1615_Locations_Spinal_Fiber_Tracts.jpg. Licensed under the Creative Commons Attribution 3.0, https://creativecommons.org/licenses/by/3.0/deed.en)

Categories of Pain in the ICU

The main categories of pain are acute pain, chronic pain, and neuropathic pain.

Acute pain refers to a predictable physiological response to a chemical, thermal, or mechanical injury caused by surgery, trauma, or acute illness [4]. While the term "acute" suggests a brief duration, persistent nociceptive signaling may perpetuate acute pain for up to 6 months [5]. Therefore, the acute terminology refers to the type and initiation phase of the pain response rather its duration. The precise location of acute somatic pain is readily identifiable and may be described as sharp or stabbing. Acute visceral pain is generally more difficult to localize and can even trigger a "referred pain" phenomenon whereby the perceived location of pain is remote from the actual source for pain. For example, myocardial infarction may be experienced as shoulder or jaw pain. Visceral pain is typically perceived a dull ache, tightness, or cramp sensation.

Chronic pain is defined as pain that is sustained beyond the period of tissue injury and healing. In this situation, abnormal signaling from peripheral somatic or visceral nociceptors persists in the absence of direct stimulus, a phenomenon attributed to maladaptive neuroplasticity within the CNS. Definitions for the minimal duration for chronic pain vary from 3 months to beyond 6 months. Patients who

experience chronic pain often develop associated anxiety and depression [6]. The symptomatology in chronic pain may have somatic, visceral, or neuropathic features. In addition, patients may experience symptoms of *allodynia*, whereby a non-noxious stimulus is perceived as pain, or *hyperalgesia* in which there is an exaggerated response to a noxious stimulus. Hyperalgesia becomes especially problematic when patients who have preexisting chronic pain syndromes experience acute pain, a phenomenon described as "acute on chronic pain" [7, 8].

Neuropathic pain results from direct injury to nerves in the peripheral or central nervous system. Neuropathic pain is described as burning or tingling in nature. Neuropathic pain can be acute or chronic. Since healing of nervous tissues occurs more slowly than in other tissues, neuropathic pain is often associated with a more sustained or chronic course. In contrast to somatic and visceral chronic pain which occur in the absence of stimulus, neuropathic pain resulting from persistent peripheral nerve injury may be considered chronic in nature [9].

Causes of Pain in the ICU

Pain experienced by patients in the intensive care unit (ICU) can be categorized as non-procedural or procedural. Non-procedural pain is the unprovoked discomfort experienced in over half of critically ill patients [10]. Procedural pain is discomfort that results from interventions which are commonly performed in the ICU. Examples include phlebotomy, invasive brain monitoring, central venous catheter placement, arterial catheterization, intubation, mechanical ventilation, naso- or orogastric tube placement, different endoscopic procedures in the lungs or gastrointestinal tract, tracheostomy, paracentesis, and chest tube insertion (reported to be the most painful of all procedures in the ICU). Additionally, routine and necessary provider care such as physical examination as well as nursing care such as bathing, turning, and bed manipulation may be extremely painful to the critically ill patient. Compared to pain at rest, procedural pain is generally more severe, estimated on average to have twice the intensity of non-procedural pain [11]. In aggregate, procedural and non-procedural pain are extremely common in the ICU and may be underreported, particularly by patients with impaired communication such as those who have brain injury or are undergoing sedation or mechanical ventilation.

A subpopulation of critically ill patients with a high likelihood of impaired communication are patients with acute brain injury. Pain in these patients may be underreported due to often lacking documentation by providers on pain assessments and/or the withholding of treatment with potentially sedating analgesics [12]. Over-sedation can mask and potentially delay the diagnosis of acute neurological changes. While this may provide a rationale to avoid analgesics, the unintended consequence is an inadequate accounting of pain and thus a high risk of insufficient analgesia in brain-injured patients [13–15].

Conversely, another common obstacle to effective assessment and treatment of pain in the ICU is excessive sedation. While the potential harms of over-sedation

and immobility are outside the scope of this chapter, overmedication with sedatives may mask pain rather than effectively treat it. Differentiating between clinical states associated with sedation and analgesia is a challenge for clinicians in the ICU. In one study, investigators evaluated postoperative patients with sedation and pain scores at set intervals. Patients who were susceptible to the sedative effects of opioids and more somnolent postoperatively reported higher pain scores than non-somnolent patients when aroused and queried, and they recalled higher postoperative pain on the following day than patients who experienced less sedation postoperatively. This study highlights the fact that behavioral evidence of sedation, even as a side effect of opioids, does not necessarily correlate with analgesia [16].

Differentiation Between Pain and Other Behavioral Syndromes

A fundamental clinical challenge for the ICU clinician is the potential for overlap between the signs of pain and other neurobehavioral states commonly encountered such as delirium, anxiety, and agitation. A comprehensive review of these topics is addressed in a recent expert consensus statement issued by the Society for Critical Care Medicine [17]. These guidelines discuss the available evidence for distinguishing these complex behavioral syndromes in order to facilitate more accurate diagnosis and treatment.

There are five criteria for the diagnosis of delirium according to the American Psychiatric Association Diagnostic and Statistical manual of Mental Disorders, fifth edition [18]. The first is a disturbance in attention. The second is that the disturbance develops over the course of hours or days and fluctuates throughout the day. The third criterion involves a change in cognition such as difficulty with memory, orientation, or language. The fourth is that the condition cannot be explained by another preexisting or developing neurocognitive disorder. The last criterion is that the condition is the result of a medical condition, substance intoxication or withdrawal, medication side effect, or due to multiple etiologies. Different screening tools are utilized clinically to assess for delirium in the ICU, the most widely implemented of which is the Confusion Assessment Method (CAM) and the Confusion Assessment Method in the ICU (CAM-ICU). According to one estimate, the CAM-ICU had a sensitivity of 83% and a specificity of 100% in detecting delirium when compared against the DSM-V as a standard (Table 2.1, Fig. 2.3) [19].

Anxiety is defined as a state of apprehension, agitation, increased motor attention, autonomic arousal, and fearful withdrawal [20]. Several diagnostic instruments have been validated to assess anxiety. Among the tools are the State-Trait Anxiety Inventory (STAI), the Profile of Mood States (POMS), the Positive and Negative Affect Schedule (PANAS), and the Visual Analog Scale (VAS-A) [21]. Unlike the widely used CAM-ICU instrument, the routine adoption of anxiety assessment tools in the ICU has been quite limited. According to one study, patients on mechanical ventilation reported variable degrees of anxiety throughout their ICU

Table 2.1 DSM-V diagnostic criteria for delirium [40]

1. A disturbance in attention
2. The disturbance develops over the course of hours or days and fluctuates throughout the day
3. A change in condition such as difficulty with memory, orientation, or language
4. The condition cannot be explained by another preexisting or developing cognitive disorder
5. The condition is not the result of a medical condition such as acute intoxication, medication side effect, or withdrawal from a medication or substance

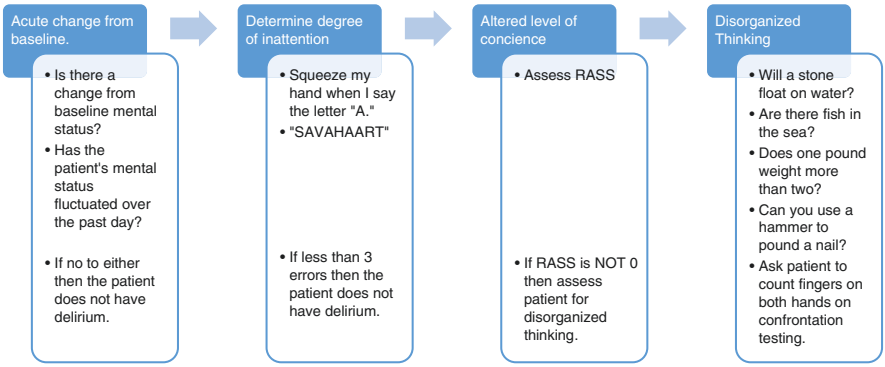

Fig. 2.3 CAM-ICU survey [41]

length of stay, without a clear pattern of resolution [22]. Recent longitudinal cohort studies of post-ICU survivors suggest an association between anxiety states in the ICU and the development of long-term post-traumatic stress disorder (PTSD) [23].

Agitation is a behavioral phenotype of dramatically increased motor activity which may be observed in a subset of critically ill patients with or without pain. The Richmond Agitation Scale (RASS) is a 10-point scale ranging from +4 indicating combative behavior, a score of 0 representing a calm alert state, and a score of −5 assigned to unarousable sedation [24]. The RASS score is a global indicator of neurobehavioral status and should not be regarded as a measure of pain.

History of Pain Scales

Initially intended as investigative tools for experimental psychology, pain scales attempted to quantify the subjective experience of pain in a burgeoning field of study called quantitative sensory testing (circa mid twentieth century). The original studies evaluated pain thresholds of test subjects by determining the amount of stimulation a human could tolerate before calling for the termination of the

stimulus. Subsequently, standardized descriptors of pain were developed by investigators to fit within various categories of pain that were being characterized. One example is the McGill Pain Questionnaire that incorporates a large selection of terms to describe pain [25]. (Table 2.2) Pain scales began to proliferate thereafter from simple four-point scales (no pain, mild, moderate, severe pain) to the 11-point numerical rating scale (NRS) (0–10) commonly used in medical practice today. By the 1960s, the visual analog scale (VAS) had been proposed to allow for the nonverbal reporting of pain. The Wong-Baker FACES® Pain Rating Scale, arguably the best known pain measurement tool, was developed for pediatric patients (Fig. 2.4). This scale was developed in the early 1980s to help children express the degree of pain they experienced irrespective of their ability to communicate verbally or abstract ability to understand the visual analog scale. Variations of the scale were subsequently applied to adults.

Table 2.2 McGill pain questionnaire descriptive terms [25]

Flickering	Tugging	Fearful	Tight
Quivering	Pulling	Frightful	Numb
Pulsing	Wrenching	Terrifying	Drawing
Throbbing	Hot	Punishing	Squeezing
Beating	Burning	Grueling	Tearing
Pounding	Scalding	Cruel	Cool
Jumping	Searing	Vicious	Cold
Flashing	Tingling	Killing	Freezing
Shooting	Itchy	Wretched	Nagging
Pricking	Smarting	Blinding	Nauseating
Boring	Stinging	Annoying	Agonizing
Drilling	Dull	Troublesome	Dreadful
Stabbing	Sore	Miserable	Torturing
Lancinating	Hurting	Intense	PPI
Sharp	Aching	Unbearable	No pain
Cutting	Heavy	Spreading	Mild
Lacerating	Tender	Radiating	Discomforting
Pinching	Taut	Penetrating	Distressing
Pressing	Rasping	Piercing	Horrible
Gnawing	Splitting		Excruciating
Cramping	Tiring		
Crushing	Exhausting		
	Sickening		
	Suffocating		
Brief	Rhythmic	Continuous	
Momentary	Periodic	Steady	
Transient	Intermittent	Constant	

Fig. 2.4 Wong-Baker FACES (Wong-Baker FACES Foundation (2020). Wong-Baker FACES® Pain Rating Scale. Retrieved [2/25/2020] with permission from http://www.WongBakerFACES.org)

Pain Scales in Current Practice

Several tools have been validated for the assessment of pain in the intensive care unit (ICU). These tools can be divided into two categories. Self-report scales are intended for patients who are able to communicate. Behavioral assessment tools are used in patients who are unable to communicate. Protocol-based pain surveys in the ICU have been associated with reductions in pain scores, opioid requirements, duration of mechanical ventilation, and ICU length of stay [26].

The most direct means of assessing a patient's pain is through verbal communication. When patient and provider share the same language, pain can be communicated and measured with the Visual Analog Scale (VAS), the Verbal Descriptor Scale (VDS), and the Numeric Rating Scale (NRS) [27] (Fig. 2.5). The VAS is administered by showing the patient a 10-cm line that is labeled with no pain on the left and worst imaginable pain on the right. On confrontation testing, the patient is asked to mark the point on the line that represents their pain. The most commonly administered VDS in the ICU attempts to categorize the spectrum of pain by offering five degrees of pain to choose from. The pain categories are typically aligned in the same direction as the VAS and include no pain, mild pain, moderate pain, severe pain, and extreme pain. The NRS covers a more granular spectrum of pain scores, typically 0 (indicating no pain) to 10 (worst pain). The VAS requires visual interaction and can be administered to patients who are intubated, while the VDS and the NRS can be administered in writing or verbally to patients who are not intubated. The verbally communicated scales offer the added benefit that they can be administered on the telephone following hospital discharge for long-term studies [28].

Behavioral assessment tools are reserved for patients who are unable to accurately or reliably report the pain they experience. The two most utilized pain scales are the Behavioral Pain Scale (BPS) for intubated and non-intubated patients and the Critical-Care Pain Observation Tool (CPOT) [29, 30]. Since the validation of these scales, several other modified scales have been reported. The Behavioral Pain Scale (BPS) was one of the original instruments intended to assess pain in nonverbal, mechanically intubated patients [29]. It evaluates three behavioral categories

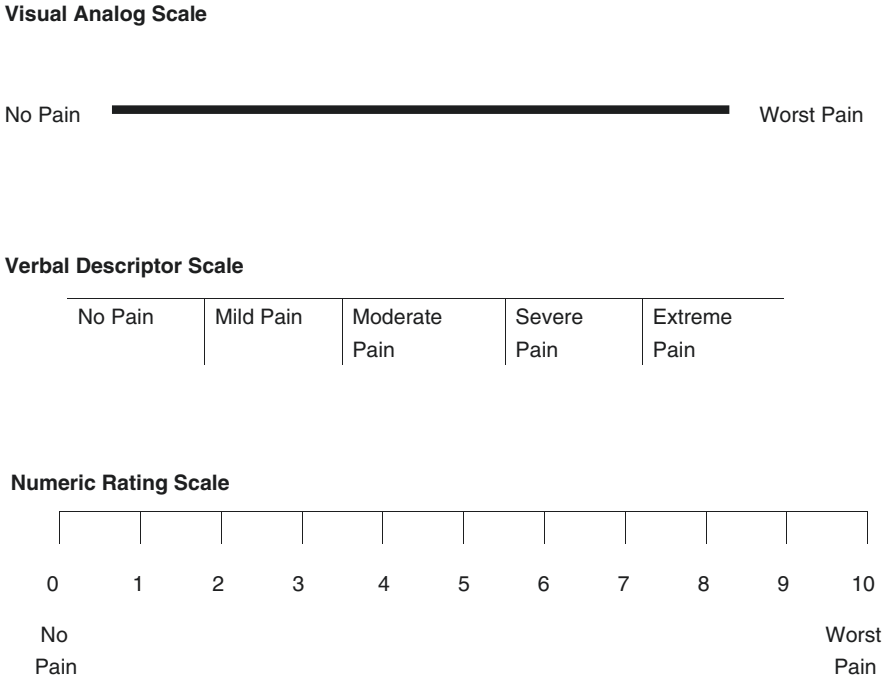

Fig. 2.5 Self-report scales

Table 2.3 Behavioral pain scale [29]

Item	Description	Score
Facial Expression	Relaxed	1
	Partially tightened (e.g., brow lowering)	2
	Fully tightened (e.g., eyelid closing)	3
	Grimacing	4
Upper Limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with Ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4
Total		3–12

and assigns a score of 1–4 for each. The categories are facial expression, movement of upper limbs, and tolerance of mechanical ventilation (Table 2.3). The CPOT is another validated instrument that assesses behavioral pain according to four categories: facial expression, body movements, muscle tension, and tolerance of the ventilator (intubated patients) or vocalization (non-intubated patients) . The categories

Table 2.4 The critical-care pain observation tool (CPOT) [30]

Indicator	Description	Score
Facial expression	No muscular tension observed	Relaxed, neutral 0
	Presence of frowning, brow lowering, orbit tightening, and levator contraction	Tense 1
	All of the above facial movements plus eyelid tightly closed	Grimacing 2
Body movements	Does not move at all (does not necessarily mean absence of pain)	Absence of movements 0
	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements	Protection 1
	Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness 2
Muscle tension evaluation by passive flexion and extension of upper extremities	No resistance to passive movements	Relaxed 0
	Resistance to passive movements	Tense, rigid 1
	Strong resistance to passive movements, inability to complete them	Very tense or rigid 2
Compliance with the ventilator (intubated patients) OR Vocalization (extubated patients)	Alarms not activated, easy ventilation	Tolerating ventilator or 0 movement
	Alarms stop spontaneously	Coughing but tolerating 1
	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator 2
	Talking in normal tone or no sound	Talking in normal tone or no sound 0
	Sighing, moaning	Sighing, moaning 1
	Crying out, sobbing	Crying out, sobbing 2
Total Range		0–8

are scored 0–2, with a range of possible sums from 0 (no pain) to 8 (extreme pain) [29, 30] (Table 2.4).

Despite the diversity of pain scales for the evaluation of patients with or without the capacity to communicate, there is a paucity of pain instruments which differentiate between the types of pain, that is, acute, neuropathic, chronic, and acute on chronic pain. This more granular degree of pain assessment has been used primarily in clinical research protocols, but it may be essential for the more precise delivery of targeted analgesics and the potential for opioid sparing analgesics.

Surrogate Indicators of Pain

In addition to the habitual pain assessment in individual ICU patients, surrogate assessments by proxy from family members, degree of opioid consumption, or by extent of physiologic perturbations have also been proposed [31, 32].

Proxy pain assessment by family members has been the subject of considerable investigation without any conclusive validation. Family members are considered inconsistent in their reporting and tend to over-estimate the degree of pain. In response, The Society for Critical Care Medicine does not endorse the substitution of family involvement for the ICU team's utilization of pain assessment tools [17, 31].

Degree of opioid consumption has been proposed as a measure of pain. Proponents of this approach argue that only the patient is aware of his or her analgesic requirements and, therefore, clinicians can measure cumulative opioid consumption as a marker for pain. Critics argue that considerable individual variability exists with respect to pain thresholds and opioid tolerance and that inference based on opioid consumption introduces a greater potential for Type I error [33]. Regardless, the use of a patient's opioid consumption as a real-time indicator of pain requires advanced statistical modeling and has also not been convincingly demonstrated.

Physiological perturbations such as tachycardia, heart rate variability, tachypnea, hypertension, diaphoresis, and mydriasis individually or in combination all serve as indicators of pain, but thus far they have not proven accurate or reliable in precisely measuring or identifying pain [17]. Nevertheless, the recent introduction of pupillometry to clinical practice has created an opportunity to study this technology as a potential marker for pain. According to one estimate, a 19% or greater change in pupillary size correlates with a Behavioral Pain Score of greater than 3 with 100% sensitivity and 77% specificity [34]. While the availability of pupillometry is not yet mainstream and not applicable to all critically ill patients in various physiologic states, the technology is at least promising for now.

At no time has the need for an alternative to verbal and behavioral pain assessment been more evident than during the COVID-19 pandemic. Since the administration of paralytics has been common practice in the management of patients with severe ARDS, clinicians have lost the ability to assess pain or the depth of sedation objectively. Concurrently, a growing consensus has emerged that critically ill patients with COVID-19 often require higher doses of analgesics and sedatives than non-COVID-19-infected patients. According to one estimate, patients with COVID-19 consume three times the amount of opioids compared to a non-COVID cohort in the ICU, albeit without any objective endpoints for titration [35]. Heart rate variability monitoring and processed EEG hold potential utility in quantifying pain and sedation in these patients, but the investigation of these modalities is just beginning to emerge [36].

Importance of Accurate Pain Phenotyping and Precision Analgesia

The end of the last century brought about an increased awareness of pain and the declaration by the Joint Commission that pain was to be measured as the fifth vital sign and treated in every patient [37]. This initiative was buttressed by the World Health Organization's (WHO) endorsement of the "pain ladder," a concept that emphasized the diligent management of pain, particularly in patients with cancer. These ambitious campaigns to increase awareness and management of pain have since been criticized as contributing to the opioid epidemic seen in the first decades of this century. As a result, many organizations including the Joint Commission and the WHO have issued revised recommendations that place greater emphasis on the risks of opioid overmedication and the risk of addiction and fatal overdose [38, 39].

Rightful concerns over the adverse effects of opioids should not however deter ICU providers from the goal of alleviating suffering at the most critical moments of patients' lives. Rather, a more precise measurement of pain and focused delivery of analgesics should be pursued within a deliberate opioid sparing strategy. The first step in this pursuit remains the meticulous evaluation of pain. However, available numerical, visual, and behavioral pain scales lack accuracy. Research is needed to discover and validate biomarkers which will expand the discriminative power of existing pain assessment tools and differentiate which patients are responsive to the analgesic effects of available treatments, as well as which patients are overly susceptible to the side effects of the same medications. This might be achieved via genotyping, serologic specimens, electrophysiologic, and imaging data that capture with higher accuracy the type and degree of pain experienced by critically ill patients, with the goal of achieving precision in analgesia.

References

1. Lummaa V, Vuorisalo T, Barr RG, Lehtonen L. Why cry? Adaptive significance of intensive crying in human infants. Evol Hum Behav. 1998;19:193–202.
2. Oertel B, Lotsch J. Genetic mutations that prevent pain: implications for future pain medication. Pharmacogenomics. 2008;9(2):179–94.
3. Carr DB, Goudas LC. Acute pain. Lancet. 1999;353(9169):2051–8.
4. Federation of State Medical Boards. Guidelines for the chronic use of opioid analgesics. 2017. Available at: https://www.fsmb.org/siteassets/advocacy/policies/opioid_guidelines_as_adopted_april-2017_final.pdf. Accessed 2 Dec 2020.
5. Merskey H, Bogduk N. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms task force on taxonomy of the International Association for the Study of Pain Seattle. Washington, DC: IASP Press; 1994.
6. Elliott TE, Renier CM, Palcher JA. Chronic pain, depression, and quality of life: correlations and predictive value of the SF-36. Pain Med. 2003;4(4):331–9.
7. Hina N, Fletcher D, Poindessous-Jazat F, Martinez V. Hyperalgesia induced by low-dose opioid treatment before orthopaedic surgery: an observational case-control study. Eur J Anaesthesiol. 2015;32(4):255–61.

8. McAnally H. Rationale for and approach to preoperative opioid weaning: a preoperative optimization protocol. Perioper Med (Lond). 2017;6:19-017-0079-y. eCollection 2017
9. Institute of Medicine . Committee on advancing pain research, care, and education. Relieving pain in America. 2011:364.
10. Chanques G, Sebbane M, Barbotte E, Viel E, Eledjam JJ, Jaber S. A prospective study of pain at rest: incidence and characteristics of an unrecognized symptom in surgical and trauma versus medical intensive care unit patients. Anesthesiology. 2007;107(5):858–60.
11. Puntillo KA, Max A, Timsit JF, Vignoud L, Chanques G, Robleda G, et al. Determinants of procedural pain intensity in the intensive care unit. The Europain(R) study. Am J Respir Crit Care Med. 2014;189(1):39–47.
12. Stoneham MD, Walters FJ. Post-operative analgesia for craniotomy patients: current attitudes among neuroanaesthetists. Eur J Anaesthesiol. 1995;12(6):571–5.
13. Gottschalk A, Berkow LC, Stevens RD, Mirski M, Thompson RE, White ED, et al. Prospective evaluation of pain and analgesic use following major elective intracranial surgery. J Neurosurg. 2007;106(2):210–6.
14. Morad AH, Winters BD, Yaster M, Stevens RD, White ED, Thompson RE, et al. Efficacy of intravenous patient-controlled analgesia after supratentorial intracranial surgery: a prospective randomized controlled trial. Clinical article. J Neurosurg. 2009;111(2):343–50.
15. Morad A, Winters B, Stevens R, White E, Weingart J, Yaster M, et al. The efficacy of intravenous patient-controlled analgesia after intracranial surgery of the posterior fossa: a prospective, randomized controlled trial. Anesth Analg. 2012;114(2):416–23.
16. Lentschener C, Tostivint P, White PF, Gentili ME, Ozier Y. Opioid-induced sedation in the postanesthesia care unit does not insure adequate pain relief: a case-control study. Anesth Analg. 2007;105(4):1143–7. table of contents
17. Devlin JW, Skrobik Y, Gelinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med. 2018;46(9):e825–73.
18. American Psychiatric Association, American Psychiatric Association. DSM-5 task force. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington, DC: American Psychiatric Association; 2013.
19. Chanques G, Ely EW, Garnier O, Perrigault F, Eloi A, Carr J, et al. The 2014 updated version of the confusion assessment method for the intensive care unit compared to the 5th version of the diagnostic and statistical manual of mental disorders and other current methods used by intensivists. Ann Intensive Care. 2018;8(1):33-018-0377-7.
20. McCartney JR, Boland RJ. Anxiety and delirium in the intensive care unit. Crit Care Clin. 1994;10(4):673–80.
21. Rossi V, Pourtois G. Transient state-dependent fluctuations in anxiety measured using STAI, POMS, PANAS or VAS: a comparative review. Anxiety Stress Coping. 2012;25(6):603–45.
22. Chlan L, Savik K. Patterns of anxiety in critically ill patients receiving mechanical ventilatory support. Nurs Res. 2011;60(3 Suppl):S50–7.
23. Parker AM, Sricharoenchai T, Raparla S, Schneck KW, Bienvenu OJ, Needham DM. Posttraumatic stress disorder in critical illness survivors: a metaanalysis. Crit Care Med. 2015;43(5):1121–9.
24. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, et al. The Richmond agitation-sedation scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166(10):1338–44.
25. Noble B, Clark D, Meldrum M, ten Have H, Seymour J, Winslow M, et al. The measurement of pain, 1945-2000. J Pain Symptom Manag. 2005;29(1):14–21.
26. Skrobik Y, Ahern S, Leblanc M, Marquis F, Awissi DK, Kavanagh BP. Protocolized intensive care unit management of analgesia, sedation, and delirium improves analgesia and subsyndromal delirium rates. Anesth Analg. 2010;111(2):451–63.

27. Hamill-Ruth RJ, Marohn ML. Evaluation of pain in the critically ill patient. Crit Care Clin. 1999;15(1):35–54. v-vi
28. Kim TK. Practical statistics in pain research. Korean J Pain. 2017;30(4):243–9.
29. Payen JF, Bru O, Bosson JL, Lagrasta A, Novel E, Deschaux I, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med. 2001;29(12):2258–63.
30. Gelinas C, Fillion L, Puntillo KA, Viens C, Fortier M. Validation of the critical-care pain observation tool in adult patients. Am J Crit Care. 2006;15(4):420–7.
31. Desbiens NA, Mueller-Rizner N. How well do surrogates assess the pain of seriously ill patients? Crit Care Med. 2000;28(5):1347–52.
32. Neice AE. Pupil size variation and pain-can the results be generalized? J Pain. 2018;19(5):569.
33. Dai F, Silverman DG, Chelly JE, Li J, Belfer I, Qin L. Integration of pain score and morphine consumption in analgesic clinical studies. J Pain. 2013;14(8):767–77.e8.
34. Lukaszewicz AC, Dereu D, Gayat E, Payen D. The relevance of pupillometry for evaluation of analgesia before noxious procedures in the intensive care unit. Anesth Analg. 2015;120(6):1297–300.
35. Kapp CM, Zaeh S, Niedermeyer S, Punjabi NM, Siddharthan T, Damarla M. The use of analgesia and sedation in mechanically ventilated patients with COVID-19 acute respiratory distress syndrome. Anesth Analg. 2020;131(4):e198–200.
36. Boselli E, Fatah A, Ledochowski S, Allaouchiche B. ANI and BIS variations in supine and prone position during closed-tracheal suction in sedated and myorelaxed ICU patients with severe COVID-19: a retrospective study. J Clin Monit Comput. 2020;6:1–7.
37. Phillips DM. JCAHO pain management standards are unveiled. Joint commission on accreditation of healthcare organizations. JAMA. 2000;284(4):428–9.
38. Baker DW. History of the joint commission's pain standards: lessons for today's prescription opioid epidemic. JAMA. 2017;317(11):1117–8.
39. World Health Organization Web statement on pain management guidance. 2019. Available at: https://www.who.int/medicines/areas/quality_safety/guide_on_pain/en/. Accessed 23 Jan 2020.
40. American Psychiatric Association, American Psychiatric Association. DSM-5 Task Force. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington, DC: American Psychiatric Association; 2013.
41. Ely, EW. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med. 2001;29(7):1370–9. https://doi.org/10.1097/00003246-200107000-00012.