

## REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

## Opioid Tolerance in Critical Illness

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**C**RITICALLY ILL PATIENTS IN THE INTENSIVE CARE UNIT (ICU) REQUIRE urgent and complex interventions that expose them to twice as many medications as the number encountered on general medical wards.<sup>1</sup> Opioids have been the mainstay of pain control and sedation in the ICU, despite substantial adverse consequences that continue to plague their use.<sup>2</sup> Long-term opioid use leads to tolerance (i.e., less susceptibility to the effects of the opioid, which can result in a need for higher and more frequent doses to achieve the same analgesic effect), physical dependence, and opioid-withdrawal symptoms during weaning and contributes to the development of chronic pain later and opioid-induced hyperalgesia (a paradoxical hypersensitivity to pain).<sup>3-5</sup> Opioid tolerance can be seen during all types of critical illnesses; the magnitude, however, seems exaggerated in patients who have had major trauma (e.g., burn injury), in patients requiring prolonged mechanical ventilation, and in pediatric patients.<sup>6-8</sup> The development of tolerance is due in part to the large doses needed to control pain in these critically ill patients. However, the inflammatory response to opioids themselves, seen in patients in the medical ICU and those in the surgical ICU, plays an important role in tolerance. This review describes the indications for opioid therapy in patients in the ICU, opioid signal transduction during short-term and long-term use, the role of inflammation and opioid-mediated innate immune responses in tolerance, and current and potential mitigation strategies for opioid tolerance. Sedative-anxiolytic drugs, which are adjuncts to analgesia, are not within the scope of this review.

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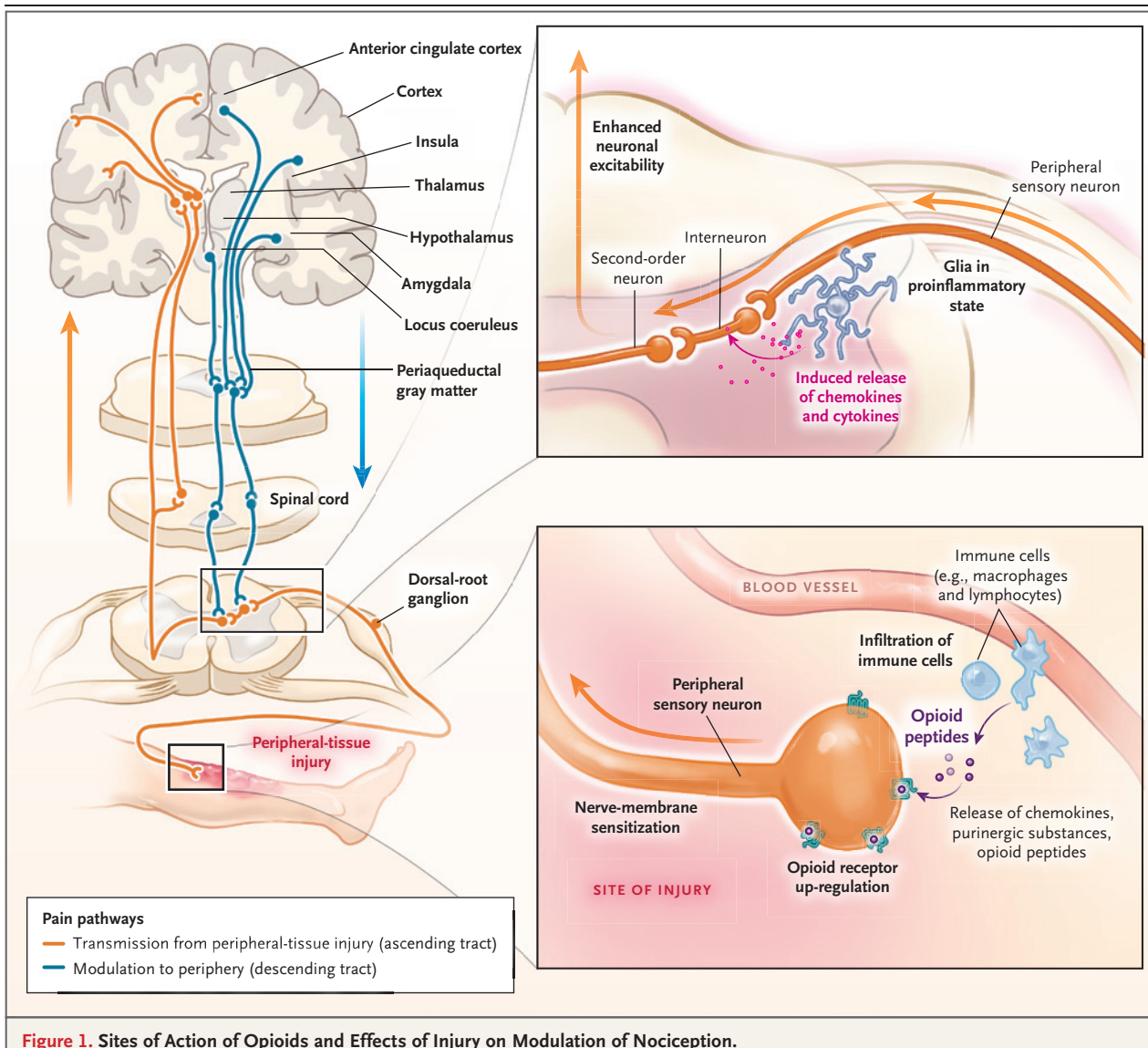
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## TISSUE AND SPINAL CORD RESPONSES TO INJURY

Most patients in the ICU have some form of tissue injury that causes local and often systemic inflammatory responses. These responses launch a cascade of events, including release of proinflammatory substances and activation of spinal cord N-methyl-D-aspartate (NMDA) receptors (Fig. 1).<sup>9</sup> Concomitantly, endogenous antinociceptive mechanisms also become operative. Centrally, the inhibitory opioidergic, serotonergic, and noradrenergic pathways are activated, which can reduce nociception. Leukocytes released at the injury site secrete endogenous opioid peptides that interact with the injury-induced opioid receptors that are up-regulated along nerve terminals and reduce pain.<sup>10</sup> However, injury-induced reduction of inhibitory control over pain by means of glycine and  $\gamma$ -aminobutyric acid receptors enhances central sensitization.<sup>11</sup> These local and central changes lead to exaggerated basal and procedural pain, referred to as hyperalgesia (exaggerated responses to painful stimuli such as a pinprick) and allodynia (pain responses to nonpainful stimuli such as touch).<sup>9,10</sup> These changes are consistent with the body's need to produce essential warning signs and withdrawal responses during nociception.



**Figure 1. Sites of Action of Opioids and Effects of Injury on Modulation of Nociception.**

Sites of action of opioids for pain relief include the brain (cortex, thalamus, hypothalamus, locus coeruleus, amygdala, and periaqueductal gray matter), spinal cord, and peripheral-nerve membrane. Transmission of pain sensation (nociception) from the peripheral-tissue injury to the central nervous system occurs through the ascending spinothalamic tract to the thalamus and then to the somatosensory cortex (orange). Descending inhibitory tracts (blue) from the brain and other regions, including the rostroventral medulla, modulate nociception. Nociception can be amplified by dorsal-root ganglia and changes in the dorsal horn of the spinal cord (top inset). The afferent neurons are sensitized by the sprouting of new axons around the cell bodies of dorsal-root ganglia, as well as by infiltrating macrophages, which release inflammatory substances. Neuron projections from dorsal-root ganglia to the dorsal horn amplify the pain by the release of other pro-nociceptive mediators (e.g., calcitonin gene-related peptide), activation of *N*-methyl-D-aspartate receptors, and the increase in glutamate levels. Second-order neurons transmit these signals upstream to the brain (orange). Injury to tissues (bottom inset) results in local and often systemic inflammatory responses, which prime the peripheral sensory neurons and dorsal-root ganglia to exaggerated nociception by up-regulation or modulation of ligand-gated and voltage-gated ion channels. Mu-opioid receptors are newly expressed throughout the nerve membrane. Extravasated circulating leukocytes (e.g., macrophages and lymphocytes) release proinflammatory mediators, further sensitizing the neurons to pain. These leukocytes also release antinociceptive endogenous opioid peptides, which bind to the up-regulated opioid receptors on the nerve, attenuating pain.

### INDICATIONS FOR OPIOID USE AND CONSEQUENCES OF INADEQUATE ANALGESIA

Moderate-to-severe pain, which generally accompanies critical illness, is often distressing and frequently underrecognized.<sup>12</sup> The underlying illness or surgery, placement of penetrating invasive tubes or catheters, and other routine intensive care procedures are recognized sources of pain.<sup>13</sup> Patients in the ICU often cannot communicate about their pain because of the combined effects of endotracheal intubation, sedation, neuromuscular blockers, altered mental status, physical restraints, and other disease-related complications. Therefore, it is imperative for caregivers to assess pain severity reliably through the use of standardized pain-assessment tools validated for use in the ICU.<sup>14</sup> Although opioids represent the primary pharmacologic therapy for moderate-to-severe pain, there are numerous other indications for opioid use, including sedation (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Analgesia-first sedation (also known as analgosedation) is a strategy for managing pain and discomfort that relies on analgesic agents first, before sedatives such as benzodiazepines. Analgesia-first sedation results in improved outcomes, including fewer days on a ventilator, as compared with combined analgesic-sedative regimens,<sup>15,16</sup> and has been recommended in clinical practice guidelines for the ICU.<sup>2</sup>

Unrelieved pain affects physiological and psychological function and is associated with both short- and long-term consequences, most of which are due to exacerbation of the stress responses induced by catecholamines, glucocorticoids, and antidiuretic-hormone release.<sup>17,18</sup> Stress activation of the hypothalamic-pituitary-adrenal axis and the renin-angiotensin-aldosterone axis can lead to fluid retention, generalized edema, and hypertension. Other adverse consequences of stress include impaired tissue oxygenation, wound healing, and immunity<sup>17,18</sup>; increased myocardial and total oxygen consumption and muscle catabolism; and neuroinflammatory priming.<sup>19-22</sup> Unrelieved pain has psychological consequences, including anxiety, depression, impaired sleep, and

demoralization, and is a risk factor for subsequent post-traumatic stress disorder.<sup>22,23</sup> Both patients and family members report pain as the most stressful experience during their time in the ICU and after discharge.<sup>24</sup> Some patients, particularly those who have undergone major surgery, have persistent pain after discharge from the ICU that contributes to a reduced quality of life.<sup>25</sup> Risk factors for the development of persistent pain are poorly controlled, high-intensity, acute pain; preoperative pain or anxiety; long-term opioid use; a relatively long ICU stay; and major surgery.<sup>26</sup>

### SIDE EFFECTS OF OPIOID THERAPY

Side effects of opioid therapy are categorized as either peripheral (e.g., constipation, urinary retention, and bronchospasm) or central (e.g., oversedation, respiratory depression, hypotension, nausea, truncal rigidity, and cough suppression). Opioid-induced vasodilatation and hypotension can increase fluid requirements after trauma.<sup>27</sup> In contrast, vasodilatation can be beneficial during disease-, anxiety-, and pain-induced hypertension. The respiratory and cough-suppressive effects can also be beneficial in the ICU setting (Table S1 in the Supplementary Appendix). Other detrimental effects that are often overlooked include inappropriate immune modulation through neuroendocrine pathways or direct effects through receptors that are present on immunocytes.<sup>28,29</sup> That opioids impair immune function has aroused concern during the care of patients with cancer in the ICU,<sup>30</sup> but the role of opioids in cancer recurrence is far from clear.<sup>31</sup> The negative effect of intolerable pain on immune function is well documented; however, the more immediate concern is the alleviation of pain and suffering and avoidance of their deleterious consequences.<sup>31</sup>

Opioids can contribute to delirium, poor sleep quality, and unintended sedation; this is particularly true in patients in the ICU, because of altered drug clearance, concomitant drug therapy, and central metabolic dysfunction. The strategy of analgesia-first sedation in trauma and burn populations in the ICU has been associated with a reduced risk of delirium,<sup>32</sup> whereas opioids

in combination with benzodiazepines, particularly in the elderly, have been associated with an increased risk of delirium.<sup>33</sup> Conversely, complete lack of sedation can result in more cases of delirium than sedation with daily interruption,<sup>34</sup> although the lack of sedation may simply result in more cases of delirium being identified.

#### PHARMACOKINETIC COMPONENTS OF OPIOID TOLERANCE

Pharmacokinetic studies of opioid use during critical illness are limited. Autoinduction of cytochrome P-450 enzyme and enhanced drug clearance do not occur with long-term opioid use and therefore cannot explain dose escalation (i.e., the need to increase the dose to maintain equipotent analgesic effects).<sup>35</sup> However, cytochrome P-450 inducers increase clearance of some drugs (e.g., methadone), resulting in subtherapeutic plasma levels, which may be misinterpreted as pharmacodynamic tolerance (i.e., tolerance due to changes in sites of action).<sup>36</sup> Similarly, during the hyperdynamic phase of trauma and compensated sepsis, the enhanced elimination kinetics of “flow dependent” drugs (e.g., fentanyl and morphine) could cause dose escalation.<sup>37</sup>

Inflammation increases the expression of  $\alpha_1$ -acid glycoprotein, an acute-phase reactant protein, which binds some drugs. Since methadone has a high affinity for  $\alpha_1$ -acid glycoprotein, there is a decreased free fraction of methadone in the plasma.<sup>36,38</sup> Despite minimal binding of fentanyl and morphine to  $\alpha_1$ -acid glycoprotein,<sup>36,38</sup> tolerance still occurs. Thus, increased glycoprotein binding contributes minimally to opioid dose escalation. The P-glycoprotein transporter that is present in brain capillaries controls drug efflux from the central nervous system. Long-term administration of oxycodone, morphine, and alfentanil, but not methadone, up-regulates P-glycoprotein expression, causing decreased drug penetration in the central nervous system and attenuated analgesia.<sup>36</sup> Similarly, tumor necrosis factor  $\alpha$  increases expression and activity of P-glycoprotein.<sup>39</sup> Together, these observations imply that critical illness-related cytokine release and opioid administration may tighten the

permeability of the P-glycoprotein-controlled blood–brain barrier, reducing the efficacy of some opioids.

#### PHARMACODYNAMIC COMPONENTS OF OPIOID TOLERANCE

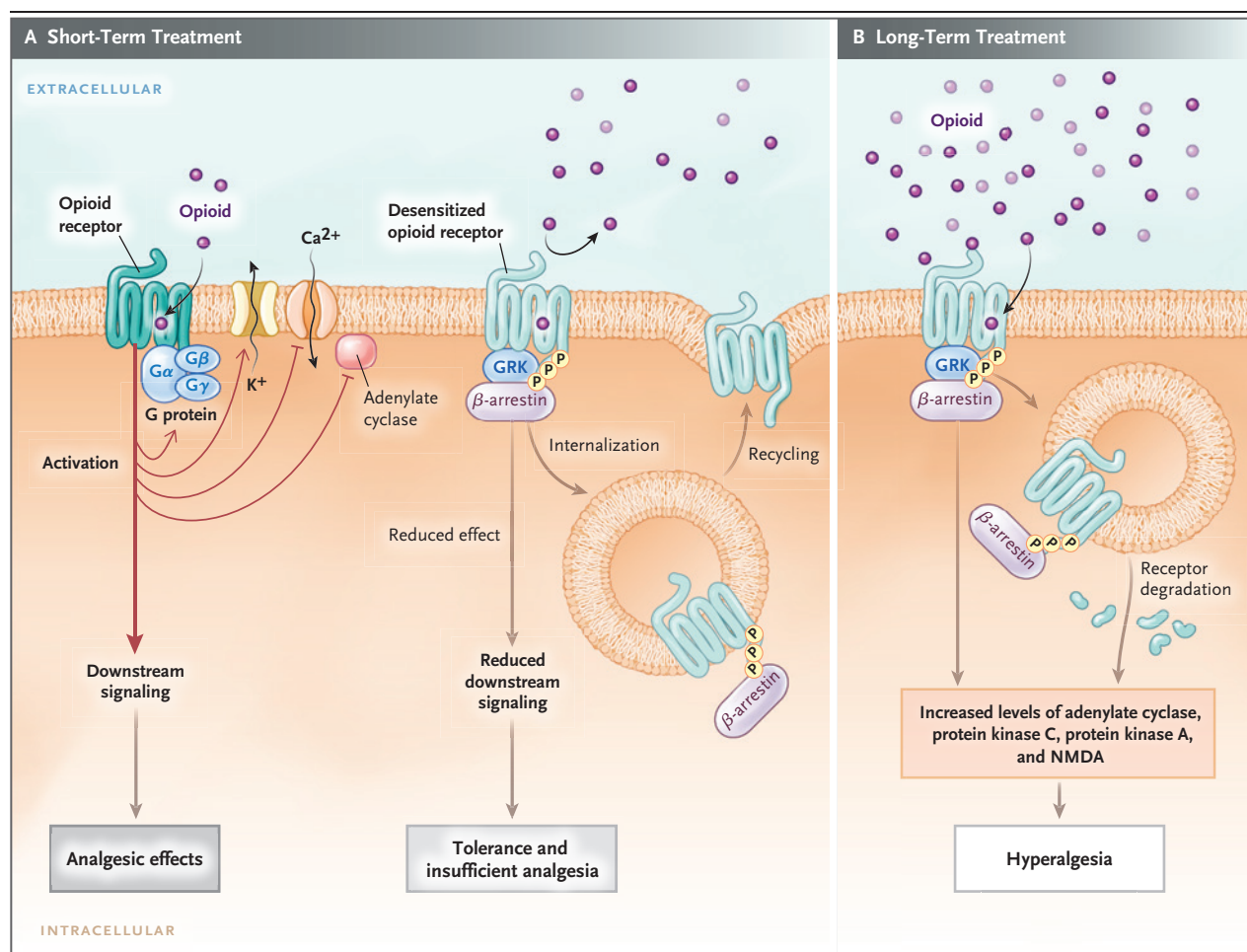
##### METABOLITE CONTRIBUTIONS

Opioid metabolism can result in metabolites that enhance or antagonize the analgesic effect or have no pharmacologic effect. In the case of morphine, the parent drug is active, although its metabolites have contrasting effects: normorphine is inactive, and morphine-6-glucuronide is more potent than morphine, whereas morphine-3-glucuronide is considered to have hyperalgesic effects that oppose the analgesic effects of morphine and of morphine-6-glucuronide.<sup>40</sup> During renal failure or dose escalation of morphine (or hydromorphone), as seen in the ICU, markedly increased morphine-3-glucuronide levels can counteract the analgesic potency of morphine and morphine-6-glucuronide.<sup>40</sup> The hyperalgesic effects of morphine-3-glucuronide are simultaneously opioid receptor-dependent and opioid receptor-independent, as shown in a study involving knockout mice<sup>41</sup> and studies involving naloxone.<sup>28</sup> The receptor-independent effects are mediated by activation of both microglia toll-like receptors and NMDA receptors.<sup>28</sup> The magnitude of the contribution of morphine-3-glucuronide to a deficiency of analgesia is controversial.

##### OPIOID-RECEPTOR SIGNALING DURING SHORT-TERM AND LONG-TERM OPIOID USE

Most clinically used opioids act through mu-opioid receptors, which belong to the G-protein-coupled receptors family, and transmit downstream signals through heterotrimeric  $G\alpha\beta\gamma$ -proteins. When an opioid binds to the mu-opioid receptor, the receptor-associated  $G\alpha\beta\gamma$ -protein dissociates into  $G\alpha$  and  $G\beta\gamma$  subunits. Concomitantly, the mu-opioid receptor becomes phosphorylated by G-protein-coupled receptor kinase,<sup>3</sup> which recruits  $\beta$ -arrestin protein and binds it to the receptor, sometimes leading to receptor internalization (Fig. 2). These processes lead to desensitization (conversion from a responsive-receptor state to a decreased-signaling state), which partly explains





**Figure 2. Opioid-Receptor Signaling during Short-Term Therapy and Long-Term Therapy.**

In short-term treatment, the binding of an opioid to its receptor (Panel A) causes downstream G-protein–coupled receptors, composed of  $\text{G}\alpha\beta\gamma$  subunits, to dissociate into  $\text{G}\alpha$  and  $\text{G}\beta\gamma$  subunits. The dissociated G-protein subunits inhibit voltage-gated calcium channels by means of reduced transmitter release, activate inward-rectifying potassium channels (causing hyperpolarization of the membrane), and inhibit downstream adenylylation enzymes, decreasing cyclic adenosine monophosphate levels. These events reduce excitability and nociception and result in analgesic effects. When an opioid binds to its receptor, it becomes an immediate substrate for phosphorylation by G-protein–coupled receptor kinase (GRK), which leads to recruitment and binding of  $\beta$ -arrestin protein to the receptor. This results in desensitization and sometimes endocytosis of the receptor; each of these events decreases the responses to opioids, inducing tolerance and insufficient analgesia. Opioid-receptor signaling terminates when the opioid is displaced from the receptor. After the stimulus (i.e., the agonist) is withdrawn, the desensitized receptor recovers over time (minutes to hours, depending on the agonist),  $\text{G}\alpha$  rebinds to  $\text{G}\beta\gamma$  and once again forms  $\text{G}\alpha\beta\gamma$ , and the endocytosed receptor is reexpressed on the plasma membrane in a resensitized state. In long-term treatment (Panel B), escalating doses of opioids and concomitant persistent activation of the receptor lead to aggravation of the tolerance by receptor-dependent and receptor-independent intracellular signaling changes, which include up-regulation of the anti-opioid (pro-nociceptive) signaling pathways. The sustained  $\beta$ -arrestin binding to the receptor often leads to internalization, degradation, and down-regulation of membrane receptor number, further decreasing response to opioids. Receptor down-regulation occurs with some opioids (e.g., fentanyl) but not others (e.g., morphine). Phosphorylation by other kinases (e.g., protein kinases A and C), increased adenylylation activity (with increased cyclic adenosine monophosphate levels), activation of *N*-methyl-D-aspartate (NMDA) receptor, and down-regulation of glutamate receptors (increased glutamate levels) are all implicated in the imbalance between pro-nociceptive and antinociceptive pathways, which results in attenuated analgesic effects, aggravated pain behaviors, increased tolerance, and opioid-induced hyperalgesia.

acute tolerance.<sup>42</sup> The desensitized receptors recover over time (minutes to hours, depending on the agonist) after the stimulus has been withdrawn, and the endocytosed receptors are recycled to the plasma membrane in a resensitized state.

Long-term opioid use leads to exaggerated opioid tolerance, which is characterized by escalating dose requirements to maintain analgesia, and subsequently contributes to opioid-induced hyperalgesia. Tolerance to the analgesic effects of opioids (and euphoria) develops faster than tolerance to respiratory depression, which explains the increased risk of hypoventilation with dose escalation during tolerance. Both duration and dose appear to affect the development of tolerance; infusions induce tolerance faster than intermittent therapy.<sup>43</sup> The potent opioid remifentanyl induces tolerance more quickly than the less potent meperidine. Persons with substance-use disorder who are receiving maintenance therapy with methadone or buprenorphine are observed to have opioid-induced hyperalgesia, which is absent in those who are not receiving opioids.<sup>44</sup>

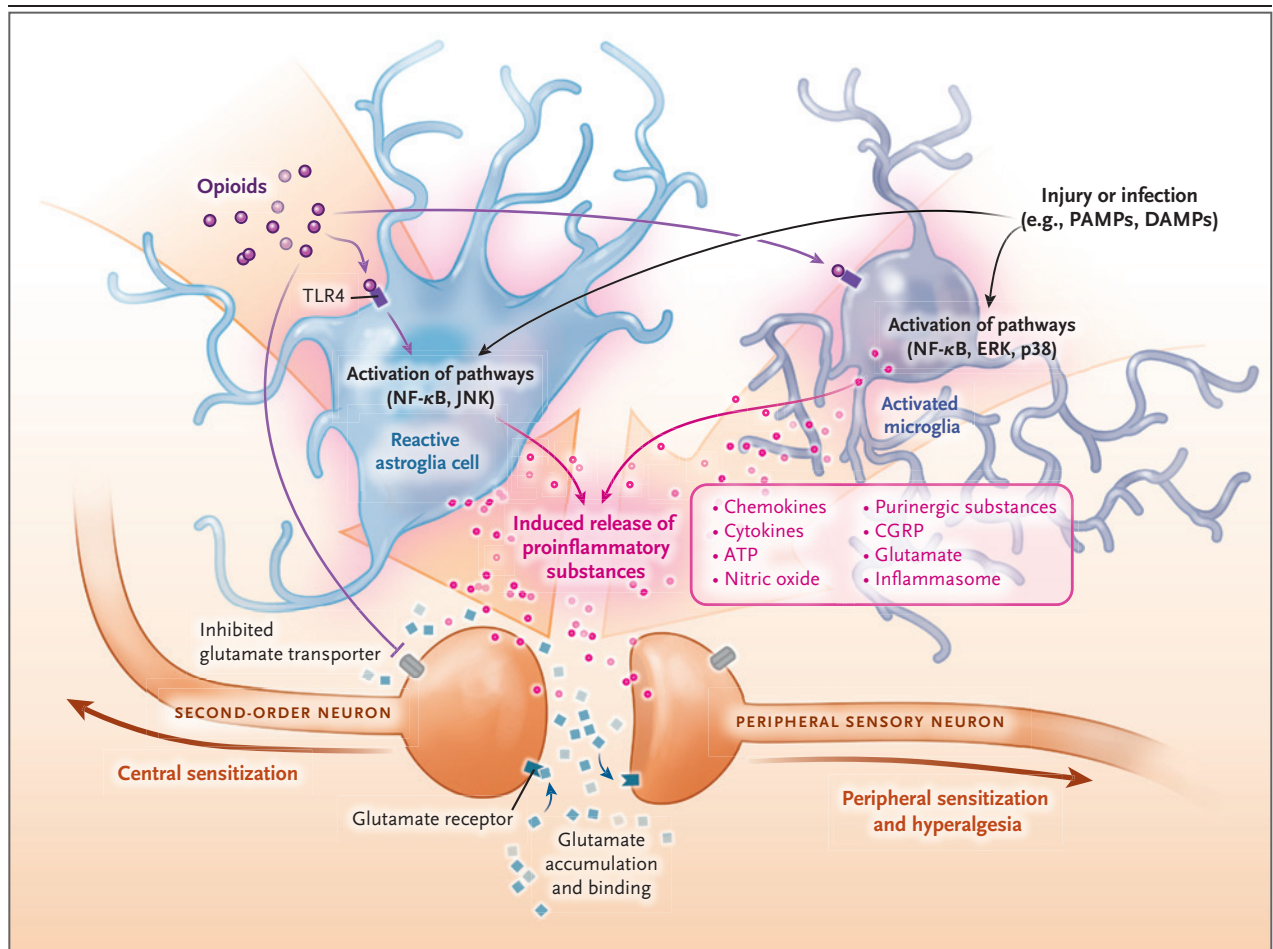
Prominent signaling changes develop during the continued presence of exogenous or endogenous ligands because the central nervous system has intrinsic mechanisms to prevent overstimulation or understimulation. The typical response of G-protein–coupled receptors to chronic agonists is receptor internalization and down-regulation together with intracellular signaling changes, leading to decreased analgesia.<sup>45,46</sup> Additional cellular adaptations during long-term opioid use include induction of systems that attenuate analgesic effects. These systems elicit adaptive responses to persistent opioid-induced inhibitory downstream signaling.<sup>45</sup> The adaptations encompass the activation of NMDA receptors, down-regulation of glutamate transporter, conversion from a state of decreased to a state of increased adenylate cyclase activity<sup>3</sup> (Fig. 2), and increased transduction through other nociception channels.<sup>3,4</sup> The formation of opioid-receptor heterodimers that bind opioids has also been implicated in opioid-induced hyperalgesia.<sup>47</sup> Thus, activation of the analgesia-attenuating system at multiple sites during long-term opioid therapy leads to an imbalance between pro-nociceptive and antinociceptive pathways, resulting in reduc-

tion of analgesia, increased tolerance, and opioid-induced hyperalgesia.

#### INNATE IMMUNE RESPONSES IN THE CENTRAL NERVOUS SYSTEM

Injury- or inflammation-related pain can become aggravated or long-lasting, features that cannot be explained by neuronal activation alone. In the central nervous system, the glia (astroglia and microglia) play a major role in central sensitization.<sup>3,28</sup> Persistent activation of the dorsal horn of the spinal cord by the injury-induced barrage of nociceptive input and the associated release of damage-associated molecular patterns (DAMPs) activate glia, which release inflammatory mediators that enhance the excitability of adjacent neurons (Fig. 3).<sup>48</sup> Although acute stress results in stress-induced analgesia, persistent sympathetic overactivity leads to stress-induced hyperalgesia.<sup>49</sup> Repetitive stress can also lead to central and peripheral leukocyte priming and release of inflammatory mediators,<sup>21,22,28</sup> causing exaggerated pain behaviors.<sup>50,51</sup> The stress-induced catecholamine surge releases immunocytes, including phenotypical inflammatory M1 monocytes (as opposed to antiinflammatory M2 monocytes). This release compounds inflammatory-mediator responses.<sup>52</sup> Stress-associated glucocorticoid release can function as DAMPs, promoting activation of the glia.<sup>22,53</sup> Superimposition of bacterial inflammation and release of pathogen-associated molecular patterns further augment leukocyte-related toll-like receptor activation and cytokine release, which can lead to nociceptor sensitization.<sup>54</sup> Systemic inflammatory diseases can also lead to neuroinflammation,<sup>55,56</sup> with selective breakdown of the blood–brain barrier to inflammatory M1 monocytes, which further exaggerate neuroinflammation, modulating both mood and nociception.<sup>20-22</sup>

Opioids, even in the absence of systemic inflammation, cause neuroinflammation by activating toll-like receptors in glia and other immune cells that permeate the blood–brain barrier.<sup>3,28,52</sup> The cytokine release from activated immune cells leads to exaggerated nociception; antagonism of toll-like receptors or their knockout in mice abrogates the hyperalgesia.<sup>28,46</sup> Similarly, specific antagonists of putative inflammatory mediators (e.g., interleukin-1 $\beta$ ) attenuate hyperalgesia. Other

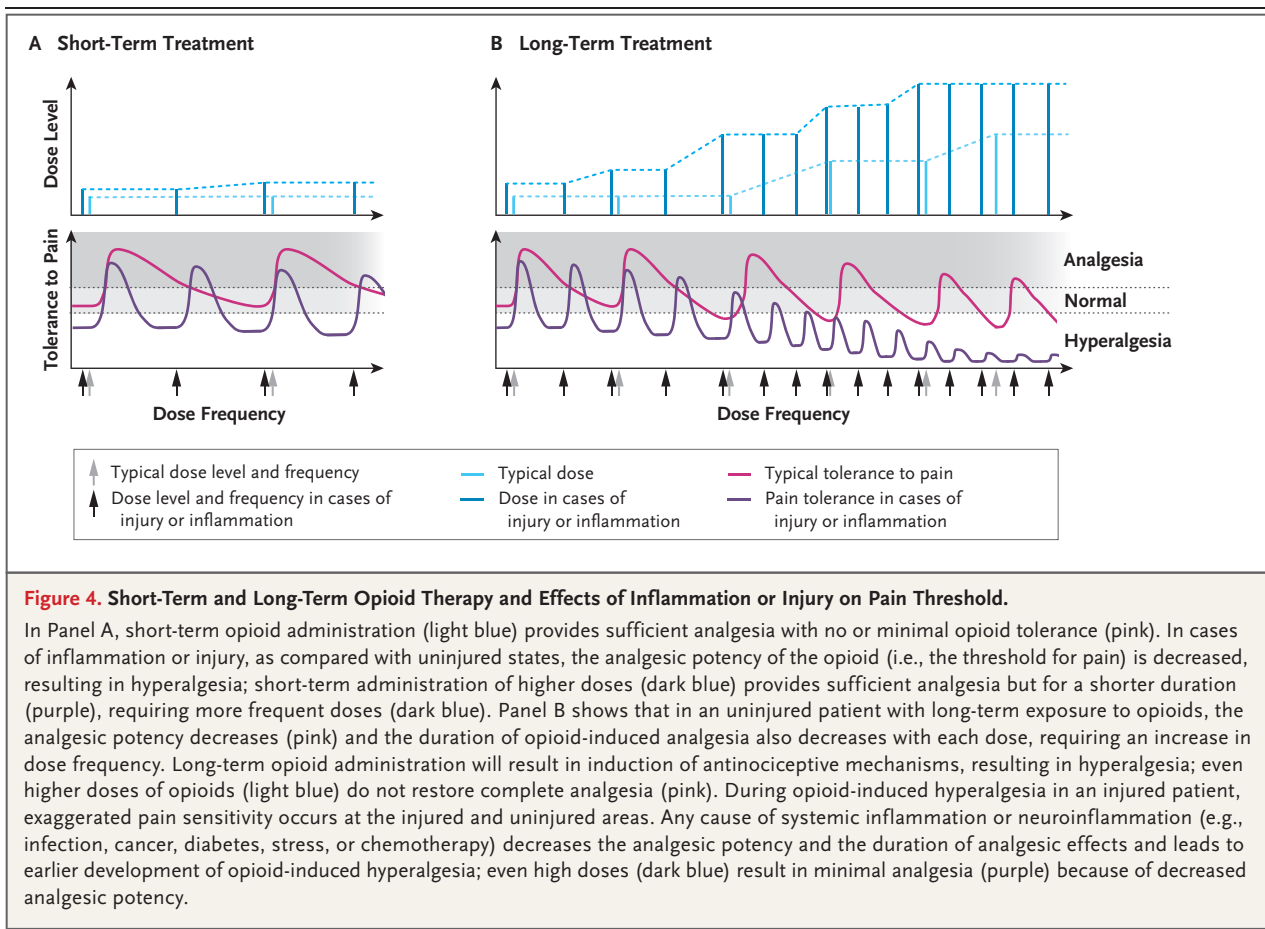


**Figure 3. Cross Talk between Neuronal and Non-Neuronal Cells during Injury and Inflammation.**

Non-neuronal cells (e.g., astroglia and microglia) can modify pain perception through the production and release of pro-nociceptive mediators. Opioids, injury, cancer, chemotherapy, stress, and other causes of sterile or microbial inflammation can induce the release of damage-associated molecular pathogens (DAMPs) and pathogen-associated molecular patterns (PAMPs). DAMPs and PAMPs cause inflammasome release, which leads to the transition of microglia to an active state and astroglia to a reactive state. The “switched on” glia release inflammatory substances through activation of toll-like receptors (TLRs) and their downstream signaling proteins (Jun N-terminal kinase [JNK], nuclear factor  $\kappa$ B [NF- $\kappa$ B], extracellular signal-regulated kinase [ERK], and p38 mitogen-activated protein kinase [p38]). Peripheral macrophages infiltrate the central nervous system because of selective breakdown of the blood–brain barrier, and they contribute to the inflammatory responses. The released proinflammatory substances (inflammasomes, ATP, and calcitonin gene-related peptide [CGRP]) sensitize the pre- and postsynaptic central neurons, leading to a vicious cycle characterized by the need for more opioids and more sensitization and more glia inflammation. The end result is a marked exaggeration of nociception, severe opioid tolerance, peripheral and central sensitization, and opioid-induced hyperalgesia.

factors that contribute to central sensitization include age, sex, and concomitant inflammatory conditions (e.g., those caused by cancer and chemotherapy). Notably, greater opioid tolerance seems to develop in pediatric patients<sup>7,8</sup>; this may be related to less inhibition in the dorsal horn and more facilitation by the rostroventral medulla than in adults.<sup>57</sup> Thus, there are multiple factors (e.g., inflammation, infection, stress,

and use of opioids) that can lead to activation of the glia in patients in the ICU and can exaggerate pain behaviors, tolerance, and opioid-induced hyperalgesia, creating a vicious cycle of dose escalation and worsening pain (Figs. 3 and 4).<sup>50,51</sup> Thus, tolerance appears to reflect a desensitization of receptor-mediated antinociceptive pathways, whereas opioid-induced hyperalgesia involves induction of pro-nociceptive glial–neuronal



pathways. Clinical observations confirm that hyperalgesia in persons with critical illnesses can be more profound than hyperalgesia in the general population.<sup>6,7</sup> Further understanding of this phenomenon should help explain why simple and routine procedures can cause pain in patients in the ICU and will allow for more empathic and better care of patients in the ICU.

and S3 in the Supplementary Appendix). Patients who have not previously received opioids usually have a good response to opioid analgesics, whereas those with prolonged exposure (illicit or prescribed) may have opioid tolerance on admission to the ICU, confounding therapy.<sup>44,58</sup> Four case scenarios are discussed in Appendix S1 and Table S4 in the Supplementary Appendix.

#### STRATEGIES TO MITIGATE OPIOID TOLERANCE AND OPIOID-INDUCED HYPERALGESIA

Strategies for mitigating opioid tolerance and opioid-induced hyperalgesia include reducing the dose of analgesics and the duration of treatment by interrupting infusions of sedative or analgesic agents daily or modulating infusions on the basis of analgesic assessment and sedation scores, by using multimodal analgesic agents (nerve blocks and nonopioid analgesics), and by rotating analgesic agents sequentially (Table 1, and Tables S2

#### DAILY INTERRUPTION OF SEDATIVE INFUSIONS

Interrupted infusions of analgesics and sedatives, as compared with uninterrupted infusions, allow patients to be more awake (without iatrogenic coma), yield improved assessment and treatment of pain with fewer days on a ventilator, lessen psychological distress, and do not increase the incidence of cardiovascular and other outcomes.<sup>59-62</sup> Conversion to intermittent bolus therapy or patient-controlled analgesia should be instituted as early as possible. Prolonged coadministration of a benzodiazepine and morphine was shown to exacerbate opioid toler-



ance<sup>63</sup>; therefore, reducing benzodiazepine use may mitigate tolerance and delirium. Alternative nonanalgesic drugs could be used for sedation and potentiation of opioid effects.

#### NEURAXIAL AND NON-NEURAXIAL ANALGESIA

Neuraxial (thoracic or lumbar epidural) analgesic techniques provide effective analgesia while reducing opioid exposure and tolerance, pulmonary morbidity, duration of mechanical ventilation, and the incidence of postoperative ileus. They also render patients more awake and able to adhere to physical therapy regimens.<sup>64,65</sup> Indications for epidurals include thoracic or major abdominal surgery, chest wall trauma, or pulmonary contusion. Despite possible contraindications in critically ill patients (e.g., administration of anticoagulant therapy), epidurals can be placed safely before — and continued during — anticoagulant administration. Other regional or non-neuraxial analgesic techniques with catheters are as effective as epidural administration of analgesics in selected patients. Non-neural blocks include paravertebral block for rib fractures or after thoracotomy, as well as transversus abdominis block for surgery of the lower abdomen.<sup>65</sup> Ultrasound-guided nerve blocks have been safely performed even in patients in the ICU who have had clinically significant coagulopathy.<sup>66</sup>

#### OPIOID ROTATION

Opioid rotation (i.e., administration of a different opioid to control pain) generally mitigates tolerance. A single gene encodes the mu-opioid receptor, but during gene expression some exons are excluded from the final messenger RNA. Consequently, several receptor subtypes can coexist (e.g.,  $\mu_1$  and  $\mu_2$ ) owing to alternative exon splicing. One receptor subtype may undergo desensitization to one opioid, leaving other subtypes available for a new opioid; hence, the rationale for opioid rotation for the restoration of analgesic efficacy and decreased doses.<sup>67</sup> During opioid rotation, the dose of the new opioid is derived empirically because opioid conversion tables (used for calculations of opioid equivalence) may be inapplicable in a patient in whom tolerance has developed, particularly during the coadministration of nonopioid adjuvants (e.g., dexmedetomidine or ketamine).<sup>67</sup> Another explanation for the efficacy of drug rotation during

**Table 1. Strategies for Mitigating Opioid Tolerance or Opioid-Induced Hyperalgesia.\***

<b>Appropriate use of opioids</b>
Use of valid assessment scales of pain before and during administration of the analgesic drug
Use of intermittent opioid therapy (oral or intravenous) rather than continuous infusions, when possible
Opioid rotation
Use of remifentanyl for short-term analgesia (because of potent induction of opioid-induced hyperalgesia), except when rapid offset of effect is required, as in evaluation of head injury
Minimal use of benzodiazepines (because of delirium and potential opioid-induced hyperalgesia associated with long-term use)
Avoidance of excessive dose escalation; supplementation of opioid with nonopioid analgesics
Addition of methadone to attenuate or delay opioid tolerance
<b>Coadministration of nonopioid analgesics as rescue therapy during procedures or to potentiate the effects of opioids</b>
N-methyl-D-aspartate receptor antagonists (ketamine)
$\alpha_2$ -Adrenergic receptor agonists (clonidine or dexmedetomidine)
Gabapentinoids (gabapentin or pregabalin)
<b>Continuous administration of nerve blocks by means of a catheter</b>
Neuraxial: thoracic or lumbar epidural blocks for thoracic, abdominal, or bilateral leg analgesia
Regional: brachial plexus block for arm analgesia; femoral or obturator block or both, with or without sciatic nerve block for lower-limb analgesia
Local: paravertebral block for rib fractures or chest-tube–associated pain; transversus abdominis block for lower abdominal surgery
<b>Prevention or reversal of opioid-induced hyperalgesia and opioid-withdrawal symptoms</b>
Tapering of opioid dose when pain score goal is achieved (10–20% dose reduction every 1–4 days)
Use of valid withdrawal assessment scales
Use of adjuncts to opioids (ketamine, dexmedetomidine, or gabapentinoids [gabapentin or pregabalin])
Use of methadone
<b>Reduction of inflammation</b>
Scheduled acetaminophen therapy
Short-term use of ketorolac†

\* The nonopioid strategies that are listed are usually used in combination with opioids; dosing regimens and routes of drug administration are provided in Tables S2 and S3 in the Supplementary Appendix.

† Other nonsteroidal antiinflammatory drugs (e.g., ibuprofen) have limited use in the intensive care unit because of cardiovascular, nephrotoxic, and gastrointestinal side effects.

morphine and hydromorphone therapy involves the properties of the morphine-3-glucuronide metabolite, which counteract the analgesic effects of morphine and morphine-6-glucuronide.<sup>40</sup> Replacing morphine and hydromorphone with an-

other opioid that has inactive metabolites (e.g., fentanyl or methadone) will decrease morphine-3-glucuronide levels, allowing more effective analgesia by the second drug.

#### MULTIMODAL ANALGESIA

In multimodal pain management, multiple non-opioid drugs can be used in combination with or in place of opioids to target various nociceptive pathways in the peripheral or central nervous system.<sup>68,69</sup> This approach produces additive and even synergistic effects of the analgesic agents and reduces the adverse effects of opioids. Only the common nonopioid analgesics available for pain control are discussed here (Table 1, and Table S3 in the Supplementary Appendix).<sup>69</sup>

Ketamine induces analgesia largely by blocking the NMDA receptors, but it also has modulatory roles by means of cholinergic, aminergic, and opioid systems.<sup>70</sup> Since NMDA-receptor hyperactivity underlies a key mechanism of opioid tolerance and opioid-induced hyperalgesia, ketamine effectively ameliorates these conditions.<sup>70</sup> Additional advantages include opioid sparing, minimal respiratory depression without psychotomimetic effects (at lower levels),<sup>69,70</sup> and the antidepressant effects of ketamine metabolites.<sup>71</sup>

Clonidine, an  $\alpha_2$ -adrenergic agonist, has modest analgesic, sedative, antihypertensive, and opioid-sparing effects and has also been used to mitigate opioid-induced hyperalgesia and withdrawal symptoms during opioid weaning.<sup>72</sup> Dexmedetomidine is more potent and has a shorter half-life than clonidine, and doses can easily be adjusted according to the response.<sup>69</sup>

The gabapentinoids gabapentin and pregabalin are commonly used adjuncts for multimodal analgesia. The involvement of multiple sites of action is probably responsible for their superior pain relief.<sup>69</sup> Common dose-related side effects include sedation, dizziness, and confusion, and their opioid potentiation can cause respiratory arrest.<sup>73</sup>

#### OTHER NONOPIOID DRUGS

Acetaminophen is a weak analgesic but is commonly incorporated in multimodal analgesic strategies for opioid sparing because it blocks the central production of prostaglandins.<sup>74</sup> Parenteral acetaminophen causes hypotension. Doses are reduced or not administered during hepatic dysfunction, malnutrition, or dehydration. The

traditional nonsteroidal antiinflammatory drugs (e.g., ibuprofen), which are nonselective cyclooxygenase inhibitors, are not conventionally used in the ICU because of their side effects. Ketorolac is effective as an opioid-sparing agent, and short-term ketorolac use does not increase postoperative bleeding.<sup>75</sup>

#### FUTURE DIRECTIONS FOR PREVENTION AND TREATMENT OF OPIOID TOLERANCE

The basic and translational development of forthcoming opioid-receptor-targeted and nonopioid-receptor-targeted pain therapies unrelated to patients in the ICU has been recently reviewed.<sup>76</sup> Several approaches presented in that review show promise for mitigating tolerance and hyperalgesia in the ICU. We will highlight three approaches.

#### MODULATION OF IMMUNE RESPONSES

Studies have suggested that inflammasome and toll-like receptor activation mediated by DAMPs critically affects the glial response to both tissue injury and opioids.<sup>3,28,48</sup> Toll-like receptor activation can be regulated by racemic naloxone or a stereoselective naloxone isomer, (+)-naloxone.<sup>28</sup> For example, dextromorphine exerts a stereoselective action over levomorphine in the activation of glia; opioid-receptor agonists, including morphine, activate toll-like receptors but are antagonized by (+)-naloxone.<sup>28</sup> Thus, (–)-naloxone and (+)-naloxone could be used to differentiate between the role of an opioid in analgesia and activation of toll-like receptors, making it possible to lessen the inflammatory responses to tissue injury and opioid exposure without antagonizing opioid-induced analgesia. Specific inflammasome inhibitors may also be used to modulate glia-mediated exaggerated nociception and opioid tolerance, without broadly inhibiting immunity.<sup>77</sup>

The neuronal  $\alpha_7$  nicotinic acetylcholine receptor agonists have been shown to attenuate microglia activation<sup>52,78</sup> and to have protective effects on inflammation induced by critical illnesses.<sup>79,80</sup> Moreover,  $\alpha_7$  nicotinic acetylcholine receptor activation attenuates inflammatory and neuropathic pain and opioid-induced hyperalgesia in rodent models.<sup>78,79,81</sup> Therefore,  $\alpha_7$  nicotinic acetylcholine receptor agonists could be useful in the reduction of both critical illness-related inflammation and pain.

### CANNABINOIDS

The role of endocannabinoids in anxiety, stress, and pain is well documented,<sup>82,83</sup> but the usefulness of exogenous cannabinoids in stress-induced hyperalgesia and opioid-sparing in patients in the ICU is unknown. In addition, cannabinoids regulate inflammatory responses in preclinical models.<sup>82</sup> The analgesic efficacy of cannabinoids, their interactions (additive or synergistic) with opioids, and their abuse potential when combined with opioids for pain control in patients in the ICU are topics for future study.

### BUPRENORPHINE WITH OR WITHOUT NALOXONE AND METHADONE

Buprenorphine, an opioid analgesic agent, is currently used (with or without naloxone) as replacement therapy in persons with substance-use disorders and for the treatment of chronic pain.<sup>84</sup> Although it is a weak analgesic for patients who do not have opioid dependency, it has shown promise in patients with opioid dependency because it reverses opioid-induced hyperalgesia.<sup>84</sup> Opioid-induced hyperalgesia is partially related to increased interaction of dynorphins with the kappa-opioid receptor; buprenorphine blocks the binding of dynorphins to the kappa-opioid receptor and attenuates opioid-induced hyperalgesia.<sup>85,86</sup> Furthermore, buprenorphine, although a partial opioid agonist, has high affinity for opioid receptors and thereby blocks other opioids from activating the same receptors. Although few studies have directly compared the analgesic effects of buprenorphine and methadone, buprenorphine may be superior in cases of renal failure because of extrarenal excretion.<sup>87</sup> Thus, pragmatic clinical protocols are needed to guide the use of buprenorphine and naloxone in patients in the ICU who are progressing toward opioid tolerance and for those already receiving buprenorphine or naloxone therapy before admission.

Methadone, another opioid analgesic, mitigates opioid-induced hyperalgesia by inhibiting NMDA receptors and serotonin-reuptake activity and blocking adenylate cyclase overactivity, which is partly responsible for the withdrawal symptoms.<sup>36,88</sup> The major downside of methadone is its variable metabolism, intra- and interindividually. During opioid rotation or opioid weaning, methadone doses must be adjusted to maintain sufficient alleviation of symptoms while avoiding side effects.<sup>88-90</sup> Oversedation and prolongation of the

cardiac QT interval can occur with cytochrome P-450 inhibitors or low magnesium levels. Methadone is used cautiously in the ICU because of its unpredictable half-life and cardiac toxicity.<sup>91,92</sup> Methadone is a racemic mixture of two stereoisomers (*l*-methadone and *d*-methadone), with *l*-methadone being 8 to 50 times as potent as *d*-methadone<sup>36</sup>; therefore, in patients in the ICU who do not have a response to other opioids, the usefulness of *l*-methadone or methadone, which produces analgesia through multiple sites of action that differ in potency, is not clear.<sup>36,88,90</sup>

### OTHER DRUGS AND CONSIDERATIONS

Lidocaine,  $\beta$ -adrenoceptor antagonists, magnesium, tricyclic antidepressants, and other drugs have been used as analgesic adjuncts to decrease opioid doses. Their long-term safety and efficacy in the ICU have not been well established in randomized, controlled trials. Selective serotonin-reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors have antinociceptive effects, but mortality is higher among patients who use them before ICU admission than among patients who do not.<sup>93</sup> Antipsychotic agents are currently used in the ICU as adjuncts to opioids, but their use has not been studied systematically. Multiple drugs are often administered simultaneously, and in cases of organ dysfunction, the altered drug disposition increases the risk of additive, synergistic, or antagonistic drug interactions, underscoring the importance of reviewing all medications.<sup>94</sup> Hepatic disease mildly affects the dispositions of morphine and fentanyl, and their elimination depends on hepatic blood flow; therefore, the drugs are useful in hepatic dysfunction but not in low-flow states.<sup>95</sup> Remifentanyl, although rapidly cleared even in cases of organ dysfunction, quickly induces tolerance and opioid-induced hyperalgesia.<sup>91</sup>

### CONCLUSIONS

There are many indications for opioid use in persons with critical illnesses. However, long-term opioid use has detrimental effects, including analgesic tolerance, which drives dose escalation and leads to opioid-induced hyperalgesia. Pain management (analgesia) in patients in the ICU, who are more vulnerable than the general population to both exaggerated tolerance and the deleterious effects of opioids, has been a challenge

for decades, and methods to mitigate the risks associated with opioid administration are unresolved. The etiologic factors (i.e., cell types and receptors, sex, extremes of age, and the underlying inflammation- and opioid-induced immune responses) that contribute to these maladaptive responses have not been well characterized and pose a barrier to improving analgesic therapy in cases of critical illness. A more nuanced understanding of the way critical illness and inflammation affect the body's response to opioids could lead to tremendous reduction in morbidity

among critically ill patients. Furthermore, the translational application of pain therapies targeted to opioid receptors and those targeted to nonopioid receptors is currently being studied in the general population and provides a road map for strategies to mitigate opioid tolerance in persons with critical illnesses.

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