Tolerance and Withdrawal From Prolonged Opioid Use in Critically Ill Children

abstract

OBJECTIVE: After prolonged opioid exposure, children develop opioid-induced hyperalgesia, tolerance, and withdrawal. Strategies for prevention and management should be based on the mechanisms of opioid tolerance and withdrawal.

PATIENTS AND METHODS: Relevant manuscripts published in the English language were searched in Medline by using search terms "opioid," "opiate," "sedation," "analgesia," "child," "infant-newborn," "tolerance," "dependency," "withdrawal," "analgesic," "receptor," and "individual opioid drugs." Clinical and preclinical studies were reviewed for data synthesis.

RESULTS: Mechanisms of opioid-induced hyperalgesia and tolerance suggest important drug- and patient-related risk factors that lead to tolerance and withdrawal. Opioid tolerance occurs earlier in the younger age groups, develops commonly during critical illness, and results more frequently from prolonged intravenous infusions of short-acting opioids. Treatment options include slowly tapering opioid doses, switching to longer-acting opioids, or specifically treating the symptoms of opioid withdrawal. Novel therapies may also include blocking the mechanisms of opioid tolerance, which would enhance the safety and effectiveness of opioid analgesia.

CONCLUSIONS: Opioid tolerance and withdrawal occur frequently in critically ill children. Novel insights into opioid receptor physiology and cellular biochemical changes will inform scientific approaches for the use of opioid analgesia and the prevention of opioid tolerance and withdrawal. *Pediatrics* 2010;125:e1208–e1225

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KEY WORDS

tolerance, withdrawal, abstinence, opiate, opioid, narcotic, stress, critical illness

ABBREVIATIONS

AC—adenylate cyclase
cAMP—cyclic adenosine monophosphate
iNOS—inducible nitric oxide synthase
PKC—protein kinase C
NMDA—*N*-methyl-D-aspartate
COMT—catechol-*O*-methyltransferase
SNP—single-nucleotide polymorphism
M6G—morphine-6-glucuronide
M3G—morphine-3-glucuronide
MNAS—Modified Narcotic Abstinence Scale
WAT-1—Withdrawal Assessment Tool 1

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TABLE 1 Definition of Terms and Underlying Mechanisms

Term	Definition	Primary Mechanism
Tolerance	Decreasing clinical effects of a drug after prolonged exposure to it	Upregulation of the cAMP pathway; desensitization of opioid receptors; other mechanisms
Dependence	A physiologic and biochemical adaptation of neurons such that removing a drug precipitates withdrawal or an abstinence syndrome	Activation of second-messenger protein kinases; changes in neurotransmitter levels; changes in neuronal networks
Withdrawal	A clinical syndrome that manifests after stopping or reversing a drug after prolonged exposure to that drug	Superactivation of AC; opioid receptor coupling to G_s protein; activation of excitatory amino acid receptors
Tachyphylaxis	Rapid loss of drug effects caused by compensatory neurophysiologic mechanisms	Exhaustion of synaptic neurotransmitters; activation of antagonist signaling systems; activation of NMDA receptors and iNOS
Addiction	A chronic, relapsing syndrome of psychological dependence and craving a drug for its psychedelic, sedative, or euphoric effects; characterized by compulsion, loss of control, and continued use of a substance despite harmful effects	Activation of dopaminergic reward systems in nucleus accumbens; mechanisms associated with tolerance and dependence

Critically ill children and neonates routinely receive opioids for analgesia and sedation to reduce pain, anxiety, agitation, and stress responses; retain monitoring devices; facilitate ventilation; and avoid secondary complications.[1–3] Prolonged opioid therapy often leads to tolerance, seen as diminishing pharmacologic effects, and is associated with opioid withdrawal when opioids are weaned or discontinued[4–8] (Table 1). Opioid withdrawal can be treated or prevented by using a variety of therapeutic approaches,[4,9] but it may be more desirable to block the mechanisms that lead to opioid tolerance.[10–12] We review here the epidemiology of opioid tolerance and withdrawal, the underlying cellular mechanisms, and novel approaches to avoiding these complications in critically ill children.

SCOPE OF THE PROBLEM

Treatment of pain is a priority for all patients,[13] especially for children because of their vulnerability and limited understanding.[14] Appropriate analgesia reduces the stress responses and improves the clinical outcomes of pediatric patients,[15–17] whereas inadequately treated pain may alter their subsequent development.[18–20] Up to 74% of children recalled their painful experiences during PICU admission.[21–23] Pain-induced agitation can endanger the stability of endotracheal tubes, vascular access devices, or other interventions that are necessary for intensive care. Unplanned extubations in children with a critical airway can be fatal.[24,25]

Overuse of these agents, however, may also have untoward consequences. Results of recent studies have suggested that critically ill patients are often oversedated, which prolongs their ventilator course and ICU stay.[26] The need to wean sedatives or treat withdrawal symptoms can also delay ICU and hospital discharge.[7]

No consensus exists regarding the optimal choice, route, or dosing of analgesic/sedative drugs in children (Table 2). The Paediatric Intensive Care Society (of the United Kingdom) recently published 20 recommendations regarding analgesia/sedation, but none of these were based on randomized clinical trials or dealt with tolerance or withdrawal.[27] The most commonly used drugs include morphine, fentanyl, midazolam, and lorazepam,[28–30] but none of these drugs have been well studied in children. Given that opioids are often used for extended periods of time, in continuous infusions as opposed to their initially intended periodic administration, and in unstudied combinations, it is likely that most drug-related complications remain unreported.

Opioid tolerance was identified from a retrospective chart review in neonates,[31] which showed fivefold increases in fentanyl infusions coupled with increases in plasma fentanyl concentrations to maintain the same clinical effect.[31,32] Total fentanyl doses of more than 1.6 mg/kg or infusions that lasted longer than 5 days led to opioid withdrawal.[31,32] Katz et al[33] reported opioid withdrawal in 13 of 23 infants on fentanyl infusions and in all those who received fentanyl for more than 9 days. Results of subsequent reports[4,31,34–38] suggested that opioid withdrawal occurs in up to 57% of PICU patients[33] and in 60% of PICUs.[39–42] Multiple studies have revealed complications[39,40] and prolonged hospitalization that resulted from opioid tolerance after critical illness.[7,41] Clearer understanding of opioid pharmacology may improve the management of opioid tolerance, dependence, and withdrawal in pediatric patients.

CELLULAR CHANGES AFTER OPIOID THERAPY

Six major categories of opioid receptors and their subtypes have been described: μ, κ, δ, nociceptin, σ, and ε (Table 3). Opioid agonists elicit

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TABLE 2 Equivalent Analgesic Doses of Opioids

Generic Name	Total Adult Dose, mg	Pediatric Dose, mg/kg	Oral/Parenteral Potency Ratio	Duration of Analgesia, h	Maximum Efficacy
Opioid analgesics used frequently in PICU patients					
Morphine	10	0.05–0.1	Low	4–5	High
Fentanyl	0.1	0.001–0.003	Low	1–1.5	High
Methadone	10	0.025–0.1	High	8–24	High
Hydromorphone	1.5	0.002–0.005	Low	4–5	High
Meperidine	60–100	0.5–1.5	Medium	2–4	High
Opioid analgesics used less frequently in PICU patients					
Oxymorphone	0.5–1.5	Insufficient data	Low	3–4	High
Sufentanil	0.02	0.0001–0.0003	Parenteral only	1–1.5	High
Alfentanil	0.3	0.01–0.05	Parenteral only	0.25–0.75	High
Remifentanil	0.003[a]	0.001–0.003[a]	Parenteral only	0.05[b]	High
Levorphanol	2–3	Insufficient data	High	4–5	High
Nalbuphine	10	0.1–0.2	Parenteral only	3–6	High
Buprenorphine	0.3	0.002–0.006	Low	4–8	High
Butorphanol	2	0.01–0.025	Parenteral only	3–4	High
Tramadol[c]	50–100	0.5–1.5	High	4–6	Moderate
Codeine	30–60	0.5–1	High	3–4	Low
Hydrocodone[c]	5–10	0.1–0.15	Medium	4–6	Moderate
Oxycodone[c]	4.5	0.1–0.2	Medium	3–4	Moderate
Propoxyphene	60–120[d]	Insufficient data	Oral only	4–5	Low
Pentazocine[c]	30–50[d]	0.5–1	Medium	3–4	Moderate

[a] Administered as a continuous infusion at 0.025–0.2 μg/kg per minute.

[b] Duration depends on a context-sensitive half-time of 3 to 4 minutes.

[c] Also available in sustained-release forms.

[d] Analgesic efficacy at this dose is not equivalent to 10 mg of morphine.

Adapted from Schumacher MA, Basbaum AI, Way WL. Chapter 31, Opioid analgesics and antagonists. In: Katzung B, Masters S, Trevor A, eds. *Basic and Clinical Pharmacology*. New York, NY: The McGrow-Hill Companies, Inc; 2009.

Classification of opioids into those used frequently and less frequently is based on unpublished data from a survey of current analgesic practices in PICUs that belong to the Eunice Kennedy Shriver National Institute of Child Health and Human Development–funded Collaborative Pediatric Critical Care Research Network (September 2007).

TABLE 3 Major Classes of Opioid Receptors

Opioid Receptor	Cellular Expression	Physiologic Effect	Endogenous Ligand
μ, μ_1, μ_2	Cortical layers III and IV, thalamic nuclei, striosomes within the striatum, periaqueductal gray, dorsal horn (lamina I and II) of the spinal cord	Supraspinal analgesia, euphoria, respiratory depression, sedation, miosis, reduced gastrointestinal motility, physical dependence	β-Endorphin, methionine- and leucine-enkephalins; endomorphin-1, endomorphin-2
κ, κ_1, κ_2, κ_3	Hypothalamic nuclei, periaqueductal gray, claustrum, dorsal horn of the spinal cord	Spinal analgesia, sedation, miosis, respiratory depression, dysphoria, inhibition of anti-diuretic hormone release	β-Endorphin, dynorphin $A_{1–17}$
δ, δ_1, δ_2	Deep cortical layers, striatum, amygdalar nuclei, pontine nuclei, olfactory bulbs	Spinal and supraspinal analgesia, dysphoria, sedation, mild psychotomimetic effects, respiratory/vasomotor control	Methionine-enkephalin, β-Endorphin
Nociceptin/orphanin FQ (ORL)	Cortex, olfactory nuclei, lateral septum, central gray, hypothalamus, pontine and interpeduncular nuclei, hippocampus, amygdala, substantia nigra, raphe magnus, locus coeruleus, spinal cord	Spinal and supraspinal analgesia, appetite, anxiety, memory processing, autonomic regulation, cardiovascular and renal functions, locomotor activity, gastrointestinal motility tolerance to μ-agonists	Nociceptin
σ	Cortex, nucleus of tractus solitarius, raphe nuclei, pontine nuclei, rostral ventrolateral medulla	Dysphoria, psychotomimetic effects, mydriasis	Sigmaphin
ϵ	Nucleus accumbens, arcuate and preoptic hypothalamic nuclei, ventromedial periaqueductal gray, locus coeruleus, medullary nuclei	Supraspinal analgesia, sedation, maturation of sperm, other functions	β-Endorphin, cholecystokinin, $endorphin_{1–27}$

physiologic, pharmacologic, or adverse effects by activating single or multiple populations of these receptors on the basis of their specific binding properties. These receptors are also activated by endogenous opioid peptides or other mediators that regulate various physiologic functions.

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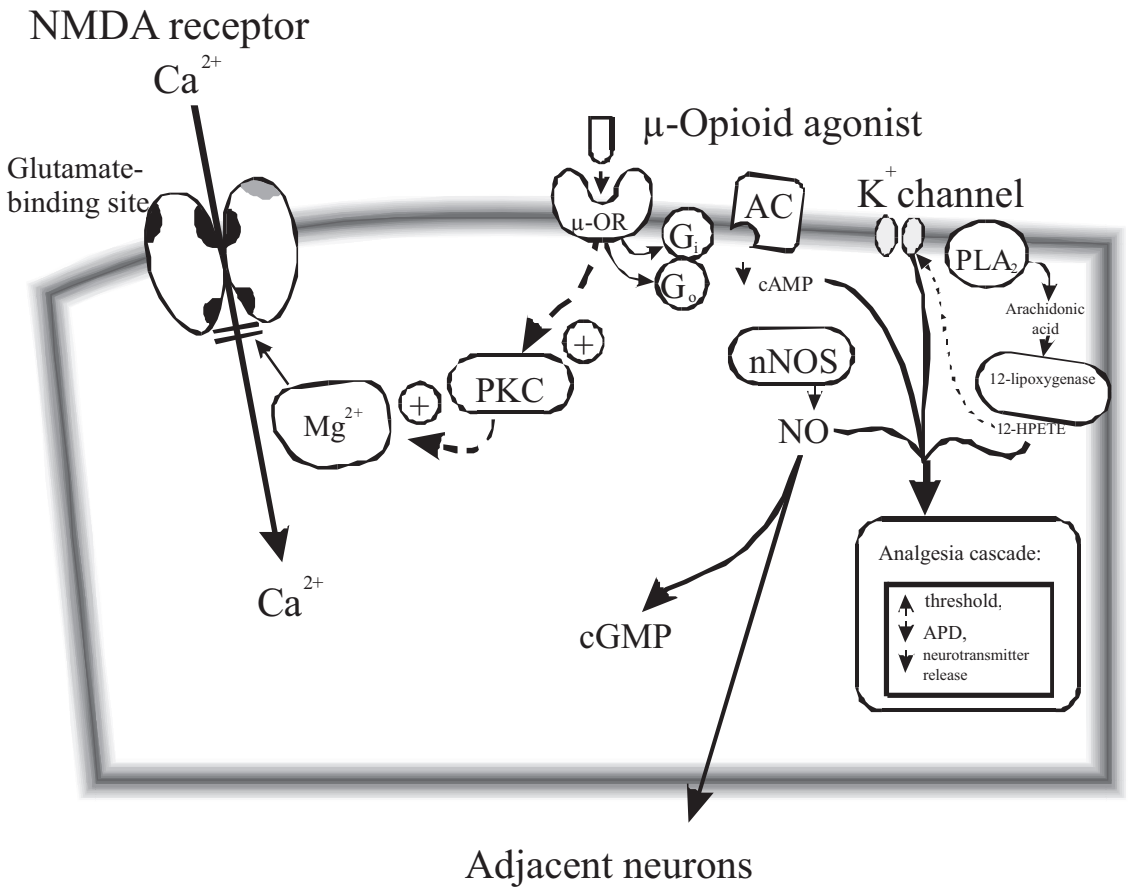

FIGURE 1

Diagrammatic representation of the neuronal mechanisms underlying opioid analgesia. Mechanisms that support the analgesia cascade increase resting membrane potential, reduce action potential duration, and decrease neurotransmitter release. μ-OR indicates μ-opioid receptor; G_i/G_o, inhibitory G proteins; nNOS, neuronal nitric oxide synthetase; NO, nitric oxide; cGMP, cyclic guanosine monophosphate; PLA_2, phospholipase A_2; APD, action potential duration; HPETE, hydroperoxyeicosatetraenoic acid.

Opioid Analgesia

Binding of specific ligands to opioid receptors leads to conformational changes in the receptor protein that initiate signal transduction with the activation of inhibitory G proteins ($G_{i2\alpha}$ and G_o). Activation of G_i protein downregulates adenylate cyclase (AC), thus reducing intracellular cyclic adenosine monophosphate (cAMP) levels, whereas G_o proteins regulate an internally rectifying K^+ channel to cause hyperpolarization of the neuronal membrane.[42] Signal transduction from activated opioid receptors lowers neuronal excitability, reduces action-potential duration, and decreases neurotransmitter release, which leads to opioid analgesia (Fig 1).

Opioid-Induced Hyperalgesia

Some opioid agonists elicit naloxone-reversible and dose-dependent excitatory effects at the opioid receptor.[10,43] These effects result from opioid receptors coupling with stimulatory G proteins (G_s), which stimulate AC, increasing cAMP and activating protein kinase A and ultimately leading to neuronal activation.[44] Neuraminidase increases these effects, whereas treatment with a neuraminidase inhibitor (eg, oseltamivir) blocks the "paradoxical" hyperalgesia caused by opioid therapy.[45]

Opioid-induced hyperalgesia occurs even in the absence of opioid tolerance (Fig 2), as demonstrated in opioid addicts, normal adult volunteers, and those who receive opioid therapy with morphine, fentanyl, remifentanil, hydrocodone, oxycodone, or methadone.[46] Finkel et al[47] postulated its occurrence in children with intractable cancer pain and successfully treated them with low-dose infusions of ketamine. Proposed mechanisms include the sensitization of primary afferent neurons, enhanced production and release of excitatory neurotransmitters, decreased reuptake of excitatory neurotransmitters, sensitization of second-order neurons, and descending facilitation from the rostral ventromedial medulla associated with upregulation of the central dynorphin and glutamatergic systems.[46,48,49]

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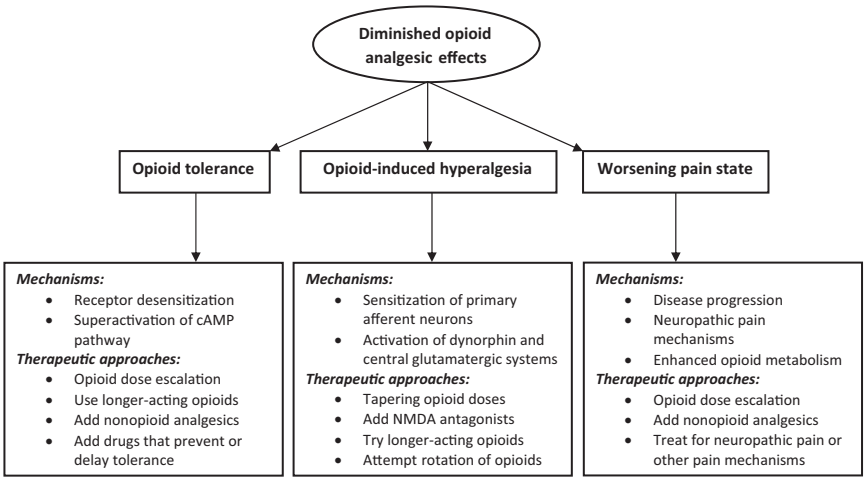

FIGURE 2

Algorithm showing that clinical signs of diminished opioid analgesia may result from developing opioid tolerance, a worsening pain state, or opioid-induced hyperalgesia. Although opioid dose escalation may overcome pharmacologic tolerance, it enhances opioid-induced hyperalgesia. Opioid-induced hyperalgesia has a generalized distribution as opposed to the localized distribution of preexisting pain, which may progress to a worsening pain state but usually responds to opioid dose escalation.

Opioid Tolerance

Although opioid-induced hyperalgesia and tolerance use similar mechanisms, (Fig 3) tolerance primarily results from receptor desensitization and upregulation of the cAMP pathway.[50,51] Other mechanisms such as neuroimmune activation,[52] production of antiopioid peptides, or activation of the spinal dynorphin system[53,54] also contribute to opioid tolerance.

Opioid receptor desensitization can be caused by (1) downregulation of opioid receptors,[55] (2) β-arrestin–mediated receptor internalization,[56,57] (3) uncoupling of opioid receptors from inhibitory G proteins,[58] (4) increased production of nitric oxide via inducible nitric oxide synthase (iNOS) activation,[59] and (5) signaling via $G_{(z)}$ proteins.[60] Upregulation of the cAMP pathway results from (1) supersensitization of AC,[51] (2) coupling of opioid receptors with G_s proteins,[43] and (3) upregulation of spinal glucocorticoid receptors[61] via a cAMP response element-binding (CREB) protein–dependent pathway,[62] which activate protein kinase Cγ (PKCγ) and *N*-methyl-D-aspartate (NMDA) receptors.

Neuronal protein kinases play a major role in opioid tolerance,[42] including (1) second messenger-dependent protein kinases (eg, PKC, calcium/calmodulin-dependent protein kinase II [CaMK-II] or protein kinase A [PKA]),[42,63] (2) G protein–coupled receptor kinases (GRKs),[64–66] (3) mitogen-activated protein kinases (MAPKs),[50,67,68] (4) extracellular signal-regulated kinases (ERK1/2),[69–72] (5) spinally expressed EphB receptor tyrosine kinases,[73] (6) the c-Jun N-terminal kinases (JNK), via expression of TRPV1 receptors,[56,74] and (7) cyclin-dependent kinase 5 (Cdk5), via regulation of mitogen-activated protein kinase kinase 1/2 (MEK1/2).[75]

Activation of these protein-kinase systems results in opioid receptor phosphorylation,[76] altered function of the ion channels involved in nociception,[77,78] increased expression of immediate early genes (eg, *FosB*),[79] and iNOS.[80,81] These protein-kinase systems are regulated by interactions between opioid receptors and the excitatory glutamate receptors,[82] γ-amino butyric acid (GABA) A receptors,[83] α_2-adrenergic receptors,[84] and cholecystokinin-B receptors.[79,85] The activation of PKC, increases in intracellular calcium ions,[57,86] and availability of postsynaptic density protein 95 (PSD-95)[87] are critical factors in the receptor interactions that lead to opioid tolerance (Fig 3).

Different opioids produce differential effects on these mechanisms, which contribute to their variable potential for producing opioid tolerance (eg, fentanyl > morphine > methadone > dihydroetorphine).[42,88] Changes in these protein-kinase systems and downstream receptor functions occur in supraspinal areas including the forebrain, striatum, thalamus, and brainstem,[89–91] as well as in the spinal cord dorsal horn,[73,74] dorsal root ganglia, and peripheral nociceptors.[55,63,77,82,92,93] Prolonged opioid exposure also activates the expression of antiopioid peptides including vasopressin, oxytocin, neuropeptide FF, cholecystokinin, or nociceptin, and mainly occurs in the spinal cord and brainstem.[94–98]

PHARMACOGENETICS OF OPIOID ANALGESIA AND TOLERANCE

Information on the genetic mechanisms that regulate these cellular changes is emerging, but their clinical importance remains to be defined.[99–101] Genetic variants affect different aspects of nociception and responses to opioid analgesia.[102–104] Altered pain perception and opioid analgesia occur from widely prevalent gene variants for (1) μ-opioid receptor (*OPRM1*),[100,105,106] (2) catechol-*O*-methyltransferase (*COMT*),[99,107,108] (3) guanosine triphosphate cyclohydrolase 1 (*GCH1*), (4) transient receptor potential cation channel, subfamily V, member 1 (*TRPV1*), and (5) the melanocortin-1 receptor (*MC1R*).[109,110] Metabolism and transport of opioids are

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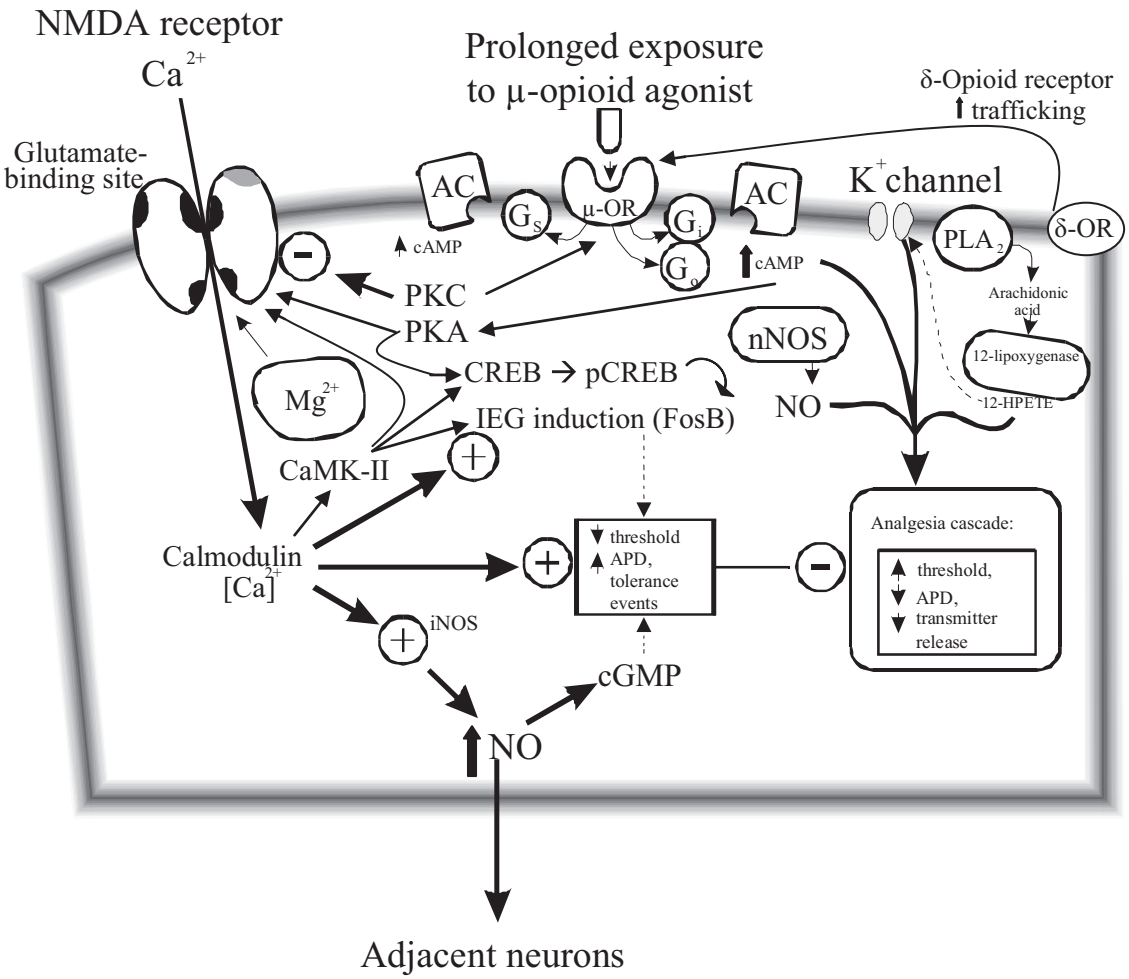

FIGURE 3

Diagrammatic representation of neuronal mechanisms underlying opioid tolerance, which decreases resting membrane potential, increases the action-potential duration (APD), and increases neurotransmitter release. μ-OR indicates μ-opioid receptor; IEG, immediate early genes (c-fos, FosB); PKA, protein kinase A; CREB, cAMP response element-binding protein; APD, action-potential duration; pCREB, phosphorylated CREB protein; G_i/G_o, inhibitory G proteins; G_s, stimulatory G protein; CaMK-II, calcium/calmodulin-dependent protein kinase II; PLA_2, phospholipase A_2; δ-OR, δ opioid receptor; NO, nitric oxide; nNOS, neuronal nitric oxide synthetase; HPETE, hydroperoxyeicosatetraenoic acid.

also affected by the genetic variants of cytochrome P450 2D6 (*CYP2D6*),[111–117] P glycoprotein (*ABCB1*),[118] and uridine diphosphate-glucuronosyltransferase 2B7 (*UGT2B7*).[119–121] With the explosion of genetic information from the Human Genome Project, thousands of single-nucleotide polymorphisms (SNPs) have been identified in opioid receptors, transport proteins, intracellular signaling proteins, and metabolic enzymes that may affect opioid analgesia and tolerance. This complexity, coupled with the difficulties in studying pediatric development,[122–126] limits the clinical utility of our knowledge. The SNPs currently known to modulate the clinical effects of analgesic drugs are listed in Table 4.

This genetic variability may explain some of the interindividual differences in analgesic requirements noted among critically ill children.[127,128] In the μ-opioid receptor gene, a nucleotide substitution at position 118 (A118G) predicts an amino acid change at codon 40, from asparagine to aspartate, which binds β-endorphin 3 times more potently than the wild-type receptor[129] and significantly reduces the potency of morphine-6-glucuronide (M6G) in humans.[130,131] It is unlikely that this SNP plays a role in opioid addiction,[132,133] but its role in opioid tolerance has not been investigated.

Opioid doses for analgesia are also reduced by an SNP of the *COMT* gene encoding the substitution of valine by methionine at codon 158,[134–137] which reduces COMT enzyme activity by three- to fourfold and is associated with greater activation of the endogenous μ-opioid system in response to pain (M158M < V158M < V158V). Pre-

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TABLE 4 SNPs That Affect Opioid Analgesia/Tolerance

Gene	Variant[a]	Frequency of Patients Affected, %[c]	Affected Analgesics (Only Drugs With Positive Evidence Are Listed)	Multiply Standard Dose by This Factor, if SNP Is Present[b]	Reference
OPRM1 (μ-opioid receptor)	118A→G exon 1	11.5	Alfentanil, morphine, M6G, methadone	2.2	102–104
	C→T intron 1	6	Morphine	>1	
	IVS2–31G→A intron 2	8.9	Morphine, M6G		
	IVS2–691C→G intron 2	44.5	No effect		
COMT (catechol-*O*-methyl transferase)	472G→A exon 4	46.2	Morphine, M6G, fentanyl	0.67[d]	105–107
MC1R (melanocortin-1 receptor)	29insA[a]	2	Morphine		108, 109
	451C→T	4.5	M6G		
	478C→T	4.3	Pentazocine (only in females)		
	880G→C	3			
CYP2D6 (cytochrome P450 2D6)	2549A→del	2	Codeine	Drug is ineffective	110–116
	1846G→A	20.7	Tramadol	1.3	
	Gene deletion	2			
	1707T→del	0.9			
	2935A→C	0.1			
	1758G→T	Rare			
	Gene amplification	2	Codeine	<1 (dosing unknown)	
ABCB1 (P glycoprotein)	3435C→T exon 1	47.6	Morphine	≪1 (less nausea)	117
	2677 G→T/A exon 3	2			
UGT2B7 (uridine diphosphate-glucuronosyltransferase 2B7)	211G→T exon 1	14.8	Morphine/M6G	Dosing unknown	118–120
	802 C→T exon 2	53.7	Morphine/M3G	Dosing unknown	
	1059 C→G exon 4	2.9			
	1062C→T exon 4	Rare			
	1192G→A exon 5	<1			

[a] The notation of the SNP is as follows: The number (eg, 118) denotes the complementary DNA position of the variant. The first letter (A, T, G, or C) denotes the most commonly found nucleotide (ie, the wild type), and the second letter denotes the nucleotide for variant alleles at this position. In case of *MC1R* 29insA, the variant is an insertion of an additional adenine after the nucleotide at complementary DNA position 29.

[b] A rough and preliminary estimate of dosing in carriers of this particular variant is based on a limited amount of quantitative data.

[c] Frequencies according to the dbSNP database (www.ncbi.nlm.nih.gov/SNP) were available and if not otherwise indicated.

[d] The factor of 0.67 = 1/1.5 comes from the ~1.5 times higher doses in wild-type patients as compared to carriers of the variant.

liminary data have suggested that this SNP reduces the need for postoperative opioid analgesia in infants[138] and adults.[139]

FACTORS THAT AFFECT DEVELOPMENT OF OPIOID TOLERANCE

Clinical and experimental data have suggested that development of opioid tolerance and dependence can be modulated by various factors. Except for duration of therapy, most of these factors have not been investigated in children.

Duration of Therapy

Duration of opioid receptor occupancy is clearly important for the development of tolerance.[31,140–143] Opioid tolerance rarely occurs after therapy for less than 72 hours.[144,145] Although continuous infusions of opioids seem to induce tolerance more rapidly than intermittent therapy,[140,141,146] a randomized trial demonstrated no significant differences between 0- to 3-year-old children who were randomly assigned to continuous versus intermittent morphine for postoperative analgesia.[147]

Early Development

Infants at early developmental stages show greater vulnerability, because opioid therapy during critical brain development may produce long-term opioid tolerance.[148,149] Indirect evidence has suggested that opioid tolerance develops earlier in preterm versus term newborns,[144,150] supported by emerging animal data.[145,148] The clinical signs of opioid withdrawal, however, are more prominent in term neonates.[151] Preterm neonates metabolize morphine to morphine-3-glucuronide (M3G) with antiopioid effects, whereas older age groups form M6G with potent analgesic effects, and both metabolites have longer half-lives than that of morphine.[152–155] M3G accumulation in preterm neonates antagonizes the effects of morphine and contributes to opioid tolerance. Developmental differences also explain why midazolam attenuates opioid tolerance in adult rats[143] but not infant rats[156] or why cotolerance to sedative and analgesic effects of fentanyl occurs in infant rats but not in adult rats.[156] Age-related differences among children in the development of opioid tolerance have not been investigated.

Gender Differences

Gender differences suggest greater development of opioid tolerance in males than in females. After 2 weeks of

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twice-daily morphine, the analgesic effective dose for 50% of subjects increased 6.9-fold in male rats versus 3.7-fold in female rats; subsequent naloxone treatment produced greater opioid withdrawal in males than in females.[157] No gender differences occurred in opioid withdrawal after exposure to morphine or fentanyl in infant rats,[145,158] but gender differences occurred in morphine analgesia after fentanyl exposure in infancy.[159] Human infants respond to aversive stimuli in a gender-specific manner,[160,161] but gender differences in opioid analgesia and tolerance have not been studied.

Drug-Related Factors

Greater tolerance occurs with the use of synthetic or short-acting opioids.[156,162] Infants who received fentanyl during extracorporeal membrane oxygenation required more supplemental analgesia, frequently developed opioid withdrawal, and required longer durations of opioid weaning compared with morphine-treated infants.[7] Drugs that cause opioid receptor internalization, decreased receptor phosphorylation by G protein–coupled receptor kinases, and less downregulation of opioid receptors are associated with less tolerance.[42] The NMDA-antagonist effects and δ-opioid receptor desensitization caused by methadone explain its lower tolerance potential compared with morphine.[76,89,163,164] Differences in opioid tolerance induced by different opioids have not been investigated systematically in infants and children.

CLINICAL MANAGEMENT OF OPIOID TOLERANCE AND WITHDRAWAL

Bedside clinicians know that the duration of opioid exposure predicts opioid tolerance. Katz et al[33] found that opioid withdrawal occurred in 100% of the patients who received fentanyl infusions for 9 days or more. Genetic and other factors are undoubtedly operative but have not been studied (see previous discussion). Opioid withdrawal must be treated aggressively by using combined pharmacologic, environmental, and nursing care approaches to decrease clinical complications and intense suffering. Therapeutic goals include reducing withdrawal symptoms, allowing regular sleep cycles, and reducing the agitation caused by medical interventions or nursing care.

Assessment of Opioid Withdrawal

Authors of a recent systematic review noted the paucity of empirically developed and validated methods for assessment of opioid withdrawal in children.[165] The neonatal abstinence syndrome has been well defined, but many of its clinical findings cannot be applied to children.[166] In older children, common neurologic signs include anxiety, agitation, grimacing, insomnia, increased muscle tone, abnormal tremors, and choreoathetoid movements. Gastrointestinal symptoms include vomiting, diarrhea, and poor appetite, whereas autonomic signs include tachypnea, tachycardia, fever, sweating, and hypertension.[167]

Previous studies of opioid withdrawal in children used the Modified Narcotic Abstinence Scale (MNAS),[7,33,34,36,41] which was originally developed for newborns of heroin-addicted mothers.[168] The MNAS was criticized for being subjective, clinically biased, and time-consuming. It included items that do not apply to children or ventilated patients, whereas other signs of the sedation-agitation spectrum (such as pupillary size[169] and responses to handling[170]) were not included. Another method, the Sedation Withdrawal Score developed by Cunliffe et al,[171] included 12 symptoms of withdrawal, each scored subjectively on a 3-point scale. The Sophia Observation Withdrawal Symptoms Scale was designed for measuring opioid and/or benzodiazepine withdrawal in ventilated patients aged 0 to 18 years.[165,167] These methods seem clinically useful, and psychometric evaluations of their sensitivity, specificity, validity, and reliability are currently underway.

Franck et al[172] developed the Opioid and Benzodiazepine Withdrawal Scale as a 21-item checklist to evaluate the frequency and severity of withdrawal symptoms. This tool was later refined to develop the 12-item Withdrawal Assessment Tool 1 (WAT-1), which was tested in 83 PICU patients. Opioid withdrawal occurred in patients with WAT-1 scores of >3, with high sensitivity (0.87) and specificity (0.88) and excellent convergent and construct validity.[172] Given its empirical development, ease of use at the patient's bedside, and psychometric properties, this method has shown the greatest promise for the assessment of opioid withdrawal in children.

Strategies for Treatment of Opioid Withdrawal

The mainstay of pharmacologic management is gradual opioid weaning. In the acute situation, most opioids are given as continuous intravenous infusions. These infusions can be substituted with long-acting enterally administered agents[35] or subcutaneous infusions,[36,173,174] which have the advantages of ease of use, decreased need for intravenous access, and early PICU discharge. Therapy must be directed by regular assessments for signs of opioid withdrawal. Pharmacologic agents commonly used to treat or prevent opiate withdrawal include the following.

1. Methadone is an effective analgesic for pediatric patients.[175,176] It has a prolonged half-life,[177,178] inhibits tolerance by multiple mechanisms,[89,164,179] and is used increas-

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TABLE 5 Methadone-Weaning Protocols After Opioid Therapy for 7 to 14 or >14 Days

Short-term Therapy Protocol (7–14 d)	Long-term Therapy Protocol (>14 d)
Use 1-h dose to convert to methadone (OD)	Use 1-h dose to convert to methadone (OD)
Day 1: give OD PO every 6 h for 24 h	Day 1: give OD PO every 6 h for 24 h
Day 2: reduce OD 20%, give PO every 8 h for 24 h	Day 2: give OD, change to PO every 6 h for 24 h
Day 3: reduce OD 20%, give PO every 8 h for 24 h	Day 3: reduce OD 20%, give PO every 6 h for 48 h
Day 4: reduce OD 20%, give PO every 12 h for 24 h	Day 5: reduce OD 20%, give PO every 8 h for 48 h
Day 5: reduce OD 20%, give PO every 24 h for 24 h	Day 7: reduce OD 20%, give PO every 12 h for 48 h
Day 6: discontinue methadone	Day 9: reduce OD 20%, give PO every 24 h for 48 h
	Day 11: discontinue methadone

Those who are converting from other opioids to methadone should take into account the relative potency (see Table 2) and duration of action of the other opioids. OD indicates original dose; PO, by mouth.
Adapted from Robertson RC, Darsey E, Fortenberry JD, Pettignano R, Hartley G. Evaluation of an opiate-weaning protocol using methadone in pediatric intensive care unit patients. *Pediatric Critical Care Medicine*. Vol 1. 2000;1(2):19–123.

ingly for opioid withdrawal in children.[34,35,180–182] A methadone dose equivalent to 2.5 times the total daily fentanyl dose was effective for preventing opioid withdrawal in children.[182] A methadone-weaning protocol, such as that depicted in Table 5, also prevented opioid withdrawal and reduced hospital stay.[41]

2. Buprenorphine is a long-acting μ-opioid partial agonist with potent analgesic properties[183–186] and naloxone-reversible[187] respiratory depression.[184,188] It is now being used as a substitute for high-dose methadone for the treatment of opioid addiction.[9,189–192] Buprenorphine was safely substituted for methadone in opioid-addicted mothers and induced less prolonged opioid withdrawal in newborns,[193–196] but it has not been studied in children.
3. Clonidine is an α_2-adrenergic receptor agonist with potent analgesic effects. Because α_2-adrenergic and μ-opioid receptors activate the same K^+ channel via inhibitory G proteins, clonidine has been used to treat opioid withdrawal in neonates,[197–199] adolescents,[13] and adults[200–202] but not in critically ill children.[203]
4. Dexmedetomidine is an α_2-adrenergic agonist with eightfold greater affinity than clonidine. It binds to α_2-adrenergic and imidazoline type 1 receptors to mediate sedative, antihypertensive, and antiarrhythmic effects. Initial reports suggested its usefulness for preventing opioid withdrawal in adults,[204,205] with increasing experience in PICU patients. Finkel et al[206,207] first reported its use in an infant with Hunter syndrome and 2 children after cardiac transplantation. Tobias reported 2 case series (7 patients each) using intravenous or subcutaneous infusions of dexmedetomidine to treat opioid withdrawal.[174,208] Additional studies are necessary to define its role in the clinical management of patients who are receiving opioids.[209]
5. Gabapentin was developed as an anticonvulsant but reduces neuropathic pain via effects on α_2-Δ calcium channels.[210,211] In adults who were undergoing rapid opioid detoxification, gabapentin effectively attenuated the severe back pain, limb thrashing, and restless-leg syndrome associated with opioid withdrawal and also changed their somatosensory evoked potentials and increased their tolerance to painful stimulation.[212] Additional studies corroborated the efficacy of gabapentin for opioid withdrawal in adults,[213–215] but it has not been tested in children.
6. Propofol can be used for preventing benzodiazepine and opioid withdrawal, as suggested by the results of preclinical and clinical studies.[216,217] In 11 children who required mechanical ventilation, propofol infusions facilitated the rapid weaning of opioid and benzodiazepine infusions, which led to successful extubation,[218] but no other studies have replicated these observations.
7. Previous case reports have suggested the utility of propoxyphene for treating morphine-induced opioid tolerance; few signs and symptoms of withdrawal and decreased respiratory depression were seen, which enabled these PICU patients to be weaned off the ventilator.[218,219] There is little cross-tolerance between morphine and propoxyphene,[220] although further evidence is required before it can be used clinically.

Other experimental agents such as memantine (a clinically available NMDA receptor antagonist[221–223]) or glycyl-L-glutamine (a naturally occurring dipeptide, produced by posttranslational processing of β-endorphin[224–226]) have been suggested as therapies for opioid withdrawal but have not been tested in pediatric patients.

Strategies for the Prevention of Opioid Tolerance

Strategies to prevent or delay opioid tolerance have the advantage of avoiding dependency and withdrawal, thereby reducing the costs and complications of prolonged opioid weaning. The true incidence of opioid tolerance and the exact strategies for preventing it remain understudied in children.

Practical Approaches

Procedural changes such as the daily interruption of sedatives,[227] nurse-controlled sedation,[228] sequential rotation of analgesics[229] (although associated with some concerns[230]), or the use of epidural/intrathecal opioids in

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pediatric patients[231–235] may decrease the incidence of opioid tolerance and withdrawal.

Nursing-Controlled Sedation Management Protocols

Adult patients who were randomly assigned to a nurse-managed sedation protocol compared with nonprotocol sedation required shorter durations of mechanical ventilation and ICU and hospital stays and less frequent tracheostomy.[228] Similar nurse-managed sedation protocols developed by Curley et al[236,237] and Sury et al[238] are currently under investigation in a cluster-randomized trial in ventilated children (Martha A. Q. Curley, personal communication, December 2008).

Use of Epidural or Other Forms of Neuraxial Analgesia

Effective analgesic doses for children are significantly reduced by epidural opioids compared with intravenous opioids. Given that the total opioid dose is a strong predictor for the occurrence of opioid withdrawal, greater use of neuraxial opioids may also reduce opioid tolerance.[232,239]

Sequential Rotation of Analgesic/Sedative Agents

The sequential use of different classes of drugs (opioids, benzodiazepines, barbiturates, butyrophenones, halogenated hydrocarbons) is recommended for analgesia and sedation in adult ICU patients to reduce the incidence of tolerance and withdrawal.[4] Although such an approach is not practical for all pediatric patients, it may be an option for PICU patients at high risk who are receiving opioid therapy for longer than 7 days.[28]

Daily Interruption of Sedative Infusions

A scheduled daily interruption of all sedative infusions in adult ICU patients (until the patients were fully awake) resulted in a shorter duration of mechanical ventilation and ICU stay.[227] This approach must be used with caution in infants and children, because awakening may cause more acute changes in their respiratory and hemodynamic variables and children are much more likely to pull out catheters and tubes than adult ICU patients.

Promising but Experimental Therapies

On the basis of the mechanisms of opioid tolerance, novel approaches for reducing or delaying its occurrence may be proposed, although the safety and efficacy of these approaches have not been investigated for critically ill children.

Concomitant Infusion of Opioid Agonists and NMDA Antagonists

NMDA receptors play multiple roles in the mechanisms that lead to opioid tolerance. Clinicians using combined intravenous infusions of morphine and low-dose ketamine (0.25–0.5 mg/kg) have noted significant opioid-sparing effects in patients with postoperative or cancer pain,[48,240–242] which supports similar findings from animal models.[243,244]

Continuous Infusions of Opioid Agonists and Low-Dose Naloxone

Low concentrations of opioid antagonists selectively block opioid receptors coupled with stimulatory G_s proteins, thus blocking mechanisms for superactivation of the cAMP pathway.[10] Three clinical trials in adults revealed that low-dose naloxone improves the efficacy of opioid analgesia and reduces tolerance,[12,187,245] although 1 trial revealed opposite effects.[246] All these studies were limited to 24 hours after surgery, a period during which the effects of opioid tolerance may not occur.[141,146] Results of a retrospective case-control study in children suggested that low-dose naloxone infusions may reduce opioid requirements,[247] but a clinical trial that was terminated early on the grounds of futility revealed no differences.[248]

Use of Noncompetitive NMDA Antagonists

Opioids such as ketobemidone[249,250] and methadone[89,163,250] block NMDA receptors and also produce less tolerance than morphine or fentanyl. Combined exposure to methadone and morphine reverses the opioid tolerance caused by morphine via a desensitization of δ-opioid receptors[164] and uncoupling of these receptors from G proteins.[179]

Use of Nitric Oxide Synthase Inhibitors

Inhibition of iNOS induction was noted to decrease the neuroadaptive changes associated with opioid dependence,[251,252] which suggests the investigation of an iNOS inhibitor, 7-nitroindazole, in clinical trials for opioid addiction.[253,254]

Use of Selective Serotonin-Reuptake Inhibitors

Preliminary data have suggested that fluoxetine may suppress the development of tolerance to morphine analgesia, which is further accentuated by L-arginine and nitro-L-arginine methyl ester treatment.[255] These results suggest a role for the nitric oxide–cyclic guanosine monophosphate–serotonin signaling system in the development of opioid tolerance and withdrawal.

Despite the availability of multiple therapies for opioid withdrawal, or practical approaches and promising experimental therapies for preventing opioid tolerance, a high incidence of opioid withdrawal still occurs in the PICU.[28,256] Randomized trials comparing these therapeutic options are needed to define their relative value for particular groups of PICU patients, thus enhancing the ability of clinicians to treat these complications of prolonged opioid exposure.

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RECOMMENDATIONS

Opioid tolerance occurs in 35% to 57% of PICU patients and often results in a prolonged hospital stay or other complications.[33,34,36,38,41,182,231] The effects of pharmacogenetic/genomic, drug-related, or patient-related factors (age, gender, diagnosis) on the development of opioid tolerance and withdrawal are currently unknown. A long-term goal is to develop therapeutic approaches that provide safe and effective opioid analgesia without inducing tolerance or withdrawal. By preventing or delaying opioid tolerance in critically ill infants and children, we can improve analgesic efficacy, avoid secondary complications, expedite recovery from critical illness, and reduce the need for prolonged intensive care support.[41,257] Specific recommendations to achieve these goals include the following.

1. Opioid doses should match the intensity and frequency of pain experienced by PICU patients, be titrated initially to achieve adequate analgesia, and be adjusted to find the minimum effective dose for each patient. Increased opioid requirements may be dictated by opioid tolerance or opioid-induced hyperalgesia or worsening pain states, each of which are treated differently (see Fig 2).
2. Short-acting opioids can be used for procedural or breakthrough pain, whereas longer-acting opioids can be used for established, prolonged, or chronic pain. Avoid using opioids if only sedation or motion control are required. Scheduled intermittent doses of longer-acting opioids may substitute for opioid infusions (see Table 2) to reduce tolerance.
3. Opioid withdrawal can be assessed by using various methods (MNAS, Sedation Withdrawal Score, Sophia Observation Withdrawal Symptoms Scale, Opioid and Benzodiazepine Withdrawal Scale). Currently, however, the WAT-1 scale seems to show the greatest promise for efficient assessment of opioid withdrawal in PICU patients.
4. Management of opioid withdrawal includes gradual opioid weaning (see Table 5), environmental and nursing supportive measures, and treatment with methadone, clonidine, or both[7] or alternative therapies such as buprenorphine, dexmedetomidine, propofol, or gabapentin.
5. Prevention of opioid tolerance may include practical approaches such as nurse-controlled sedation or sequential rotation of analgesics, although promising experimental therapies include opioids combined with low-dose ketamine or naloxone or other classes of drugs.

Critically ill children routinely receive opioids for pain management; this treatment often leads to opioid tolerance and withdrawal, both of which occur more commonly in infants and children because of developmental changes in metabolism, excretion, or dose/response curves, receptor subtypes, signal transduction, receptor induction, and regulatory pathways. Advances in opioid pharmacology cannot be applied to critically ill children, because the incidence and risk factors for opioid tolerance in PICU patients remain unknown. We need prospective observational studies to define the current incidence and risk factors for opioid tolerance in critically ill children, as well as randomized trials to compare the various therapies available for prevention and treatment of opioid withdrawal.

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