Published in final edited form as:

Pediatrics. 2010 May ; 125(5): e1208–e1225. doi:10.1542/peds.2009-0489.

Tolerance and Withdrawal From Prolonged Opioid Use in Critically Ill Children

Kanwaljeet J. S. Anand, MBBS, DPhil^a, Douglas F. Willson, MD^b, John Berger, MD^c, Rick Harrison, MD^d, Kathleen L. Meert, MD^e, Jerry Zimmerman, MD, PhD^f, Joseph Carcillo, MD^g, Christopher J. L. Newth, MD, FRCPC^h, Parthak Prodhon, MDⁱ, J. Michael Dean, MD^j, and Carol Nicholson, MD^k for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network

^aDepartment of Pediatrics, Le Bonheur Children's Hospital and University of Tennessee Health Science Center, Memphis, Tennessee ^bDepartment of Pediatrics & Anesthesiology, University of Virginia Children's Hospital, Charlottesville, Virginia ^cDepartment of Pediatrics, Children's National Medical Center, Washington, DC ^dDepartment of Pediatrics, University of California at Los Angeles, Los Angeles, California ^eDepartment of Pediatrics, Children's Hospital of Michigan, Detroit, Michigan ^fDepartment of Pediatrics, Children's Hospital and Medical Center, Seattle, Washington ^gDepartment of Critical Care Medicine, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania ^hDepartment of Pediatrics, Children's Hospital Los Angeles, Los Angeles, California ⁱDepartment of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, Arkansas ^jDepartment of Pediatrics, University of Utah School of Medicine, Salt Lake City, Utah ^kPediatric Critical Care and Rehabilitation Program, National Center for Medical Rehabilitation Research (NCMR), Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland

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

Copyright © 2010 by the American Academy of Pediatrics

Address correspondence to Kanwaljeet J. S. Anand, MBBS, DPhil, Le Bonheur Children's Medical Center, Room 4624, 50 N Dunlap St, Memphis, TN 38103. anandsunny@uams.edu.

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

scientific approaches for the use of opioid analgesia and the prevention of opioid tolerance and withdrawal.

Keywords

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

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 al³³ 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 patients³³ 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 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.

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 down-regulates 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, remifentanyl, hydrocodone, oxycodone, or methadone.⁴⁶ Finkel et al⁴⁷ 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 re-uptake 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}

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_{12} 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 receptors⁶¹ via a cAMP response element-binding (CREB) protein-dependent pathway,⁶² which activate protein kinase C γ (PKC γ) 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 (*MCR1*).^{109,110} Metabolism and transport of opioids are 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 receptor¹²⁹ 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). Preliminary data have suggested that this SNP reduces the need for postoperative opioid analgesia in infants¹³⁸ 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 rats¹⁴³ but not infant rats¹⁵⁶ or why co-tolerance 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 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 al³³ 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 size¹⁶⁹ and responses to handling¹⁷⁰) 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 al¹⁷² 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 agents³⁵ 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 increasingly 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-reversible¹⁸⁷ 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 analgesics²²⁹ (although associated with some concerns²³⁰), or the use of epidural/intrathecal opioids in 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 al²³⁸ 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 receptors¹⁶⁴ 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.

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 longterm 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 both⁷ 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.

Acknowledgments

Funded by the National Institutes of Health (NIH).

This work was supported by Eunice Kennedy Shriver National Institute of Child Health and Human Development cooperative agreements U10HD050096, U10HD049981, U10HD500009, U10HD-049945, U10HD049983, U10HD050012, and U01HD049934. We thank Pam Cate and Kris Dudoich for administrative assistance.

ABBREVIATIONS

AC	adenylate cyclase
cAMP	cyclic adenosine monophosphate
iNOS	inducible nitric oxide synthase
PKC	protein kinase C
NMDA	<i>N</i> -methyl-D-aspartate
COMT	catechol- <i>O</i> -methyltransferase
SNP	single-nucleotide polymorphism
M6G	morphine-6-glucuronide
M3G	morphine-3-glucuronide

MNAS	Modified Narcotic Abstinence Scale
WAT-1	Withdrawal Assessment Tool 1

References

1. Berde CB, Sethna NF. Analgesics for the treatment of pain in children. *N Engl J Med*. 2002; 347(14):1094–1103. [PubMed: 12362012]
2. Chambliss CR, Anand KJS. Pain management in the pediatric intensive care unit. *Curr Opin Pediatr*. 1997; 9(3):246–253. [PubMed: 9229164]
3. Anand KJS. Relationships between stress responses and clinical outcome in newborns, infants, and children. *Crit Care Med*. 1993; 21(9 suppl):S358–S359. [PubMed: 8365225]
4. Tobias JD. Tolerance, withdrawal, and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care unit. *Crit Care Med*. 2000; 28(6):2122–2132. [PubMed: 10890677]
5. Anand KJS. International Evidence-Based Group for Neonatal Pain. Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med*. 2001; 155(2):173–180. [PubMed: 11177093]
6. Anand KJS, Ingraham J. Tolerance, dependence, and strategies for compassionate withdrawal of analgesics and anxiolytics in the pediatric ICU. *Crit Care Nurse*. 1996; 16(6):87–93. [PubMed: 9004606]
7. Franck LS, Vilardi J, Durand D, Powers R. Opioid withdrawal in neonates after continuous infusions of morphine or fentanyl during extracorporeal membrane oxygenation. *Am J Crit Care*. 1998; 7(5):364–369. [PubMed: 9740886]
8. Suresh S, Anand KJS. Opioid tolerance in neonates: a state-of-the-art review. *Paediatr Anaesth*. 2001; 11(5):511–521. [PubMed: 11696114]
9. Krantz MJ, Mehler PS. Treating opioid dependence: growing implications for primary care. *Arch Intern Med*. 2004; 164(3):277–288. [PubMed: 14769623]
10. Crain SM, Shen KF. Antagonists of excitatory opioid receptor functions enhance morphine's analgesic potency and attenuate opioid tolerance/dependence liability. *Pain*. 2000; 84(2–3):121–131. [PubMed: 10666516]
11. Crain SM, Shen KF. Modulatory effects of Gs-coupled excitatory opioid receptor functions on opioid analgesia, tolerance, and dependence. *Neurochem Res*. 1996; 21(11):1347–1351. [PubMed: 8947924]
12. Gan TJ, Ginsberg B, Glass PS, Fortney J, Jhaveri R, Perno R. Opioid-sparing effects of a low-dose infusion of naloxone in patients administered morphine sulfate. *Anesthesiology*. 1997; 87(5):1075–1081. [PubMed: 9366459]
13. Colvin LA, Lambert DG. Pain medicine: advances in basic sciences and clinical practice. *Br J Anaesth*. 2008; 101(1):1–4. [PubMed: 18556695]
14. Howard RF. Current status of pain management in children. *JAMA*. 2003; 290(18):2464–2469. [PubMed: 14612483]
15. Anand KJS, Hickey PR. Halothane-morphine compared with high-dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. *N Engl J Med*. 1992; 326(1):1–9. [PubMed: 1530752]
16. Barker DP, Rutter N. Stress, severity of illness, and outcome in ventilated preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 1996; 75(3):F187–F190. [PubMed: 8976685]
17. Quinn MW, Otoo F, Rushforth JA, et al. Effect of morphine and pancuronium on the stress response in ventilated preterm infants. *Early Hum Dev*. 1992; 30(3):241–248. [PubMed: 1468386]
18. Grunau RE, Haley DW, Whitfield MF, Weinberg J, Yu W, Thiessen P. Altered basal cortisol levels at 3, 6, 8 and 18 months in infants born at extremely low gestational age. *J Pediatr*. 2007; 150(2):151–156. [PubMed: 17236892]

19. Holsti L, Weinberg J, Whitfield MF, Grunau RE. Relationships between adrenocorticotrophic hormone and cortisol are altered during clustered nursing care in preterm infants born at extremely low gestational age. *Early Hum Dev.* 2007; 83(5):341–348. [PubMed: 16979857]
20. Whitfield MF, Grunau RV, Holsti L. Extremely premature (< or = 800 g) schoolchildren: multiple areas of hidden disability. *Arch Dis Child Fetal Neonatal Ed.* 1997; 77(2):F85–F90. [PubMed: 9377151]
21. Karande S, Kelkar A, Kulkarni M. Recollections of Indian children after discharge from an intensive care unit. *Pediatr Crit Care Med.* 2005; 6(3):303–307. [PubMed: 15857529]
22. Playfor SD, Thomas DA, Choonara II. Recall following paediatric intensive care. *Paediatr Anaesth.* 2000; 10(6):703–704. [PubMed: 11119241]
23. Playfor S, Thomas D, Choonara I. Recollection of children following intensive care. *Arch Dis Child.* 2000; 83(5):445–448. [PubMed: 11040158]
24. da Silva PS, de Aguiar VE, Neto HM, de Carvalho WB. Unplanned extubation in a paediatric intensive care unit: impact of a quality improvement programme. *Anaesthesia.* 2008; 63(11):1209–1216. [PubMed: 19032255]
25. Sadowski R, Dechert RE, Bandy KP, et al. Continuous quality improvement: reducing unplanned extubations in a pediatric intensive care unit. *Pediatrics.* 2004; 114(3):628–632. [PubMed: 15342831]
26. Ostermann ME, Keenan SP, Seiferling RA, Sibbald WJ. Sedation in the intensive care unit: a systematic review. *JAMA.* 2000; 283(11):1451–1459. [PubMed: 10732935]
27. Playfor S, Jenkins I, Boyles C, et al. Consensus guidelines on sedation and analgesia in critically ill children. *Intensive Care Med.* 2006; 32(8):1125–1136. [PubMed: 16699772]
28. Jenkins IA, Playfor SD, Bevan C, Davies G, Wolf AR. Current United Kingdom sedation practice in pediatric intensive care. *Paediatr Anaesth.* 2007; 17(7):675–683. [PubMed: 17564650]
29. Long D, Horn D, Keogh S. A survey of sedation assessment and management in Australian and New Zealand paediatric intensive care patients requiring prolonged mechanical ventilation. *Aust Crit Care.* 2005; 18(4):152–157. [PubMed: 18038536]
30. Sarkar S, Schumacher RE, Baumgart S, Donn SM. Are newborns receiving premedication before elective intubation? *J Perinatol.* 2006; 26(5):286–289. [PubMed: 16598295]
31. Arnold JH, Truog RD, Orav EJ, Scavone JM, Hershenon MB. Tolerance and dependence in neonates sedated with fentanyl during extracorporeal membrane oxygenation. *Anesthesiology.* 1990; 73(6):1136–1140. [PubMed: 2248393]
32. Arnold JH, Truog RD, Scavone JM, Fenton T. Changes in the pharmacodynamic response to fentanyl in neonates during continuous infusion. *J Pediatr.* 1991; 119(4):639–643. [PubMed: 1919898]
33. Katz R, Kelly HW, Hsi A. Prospective study on the occurrence of withdrawal in critically ill children who receive fentanyl by continuous infusion. *Crit Care Med.* 1994; 22(5):763–767. [PubMed: 8181283]
34. Tobias JD, Schleien CL, Haun SE. Methadone as treatment for iatrogenic narcotic dependency in pediatric intensive care unit patients. *Crit Care Med.* 1990; 18(11):1292–1293. [PubMed: 1977561]
35. Tobias JD, Deshpande JK, Gregory DF. Outpatient therapy of iatrogenic drug dependency following prolonged sedation in the pediatric intensive care unit. *Intensive Care Med.* 1994; 20(7):504–507. [PubMed: 7995868]
36. Tobias JD. Subcutaneous administration of fentanyl and midazolam to prevent withdrawal after prolonged sedation in children. *Crit Care Med.* 1999; 27(10):2262–2265. [PubMed: 10548218]
37. Tobias JD, Berkenbosch JW. Tolerance during sedation in a pediatric ICU patient: effects on the BIS monitor. *J Clin Anesth.* 2001; 13(2):122–124. [PubMed: 11331172]
38. Fonsmark L, Rasmussen YH, Carl P. Occurrence of withdrawal in critically ill sedated children. *Crit Care Med.* 1999; 27(1):196–199. [PubMed: 9934916]
39. Bergman I, Steeves M, Burckart G, Thompson A. Reversible neurologic abnormalities associated with prolonged intravenous midazolam and fentanyl administration. *J Pediatr.* 1991; 119(4):644–649. [PubMed: 1919899]

40. Lane JC, Tennison MB, Lawless ST, Greenwood RS, Zaritsky AL. Movement disorder after withdrawal of fentanyl infusion. *J Pediatr.* 1991; 119(4):649–651. [PubMed: 1919900]
41. Robertson RC, Darsey E, Fortenberry JD, Pettignano R, Hartley G. Evaluation of an opiate-weaning protocol using methadone in pediatric intensive care unit patients. *Pediatr Crit Care Med.* 2000; 1(2):119–123. [PubMed: 12813261]
42. Liu JG, Anand KJS. Protein kinases modulate the cellular adaptations associated with opioid tolerance and dependence. *Brain Res Brain Res Rev.* 2001; 38(1–2):1–19. [PubMed: 11750924]
43. Crain SM, Shen KF. Modulation of opioid analgesia, tolerance and dependence by Gs-coupled, GM1 ganglioside-regulated opioid receptor functions. *Trends Pharmacol Sci.* 1998; 19(9):358–365. [PubMed: 9786023]
44. Crain SM, Shen KF. Ultra-low concentrations of naloxone selectively antagonize excitatory effects of morphine on sensory neurons, thereby increasing its antinociceptive potency and attenuating tolerance/dependence during chronic cotreatment. *Proc Natl Acad Sci U S A.* 1995; 92(23):10540–10544. [PubMed: 7479836]
45. Crain SM, Shen KF. Neuraminidase inhibitor, oseltamivir blocks GM1 gangliosideregulated excitatory opioid receptor-mediated hyperalgesia, enhances opioid analgesia and attenuates tolerance in mice. *Brain Res.* 2004; 995(2):260–266. [PubMed: 14672816]
46. Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. *Clin J Pain.* 2008; 24(6):479–496. [PubMed: 18574358]
47. Finkel JC, Pestieau SR, Quezado ZM. Ketamine as an adjuvant for treatment of cancer pain in children and adolescents. *J Pain.* 2007; 8(6):515–521. [PubMed: 17434801]
48. Luginbühl M, Gerber A, Schnider TW, Petersen-Felix S, Arendt-Nielsen L, Curatolo M. Modulation of remifentanyl-induced analgesia, hyperalgesia, and tolerance by small-dose ketamine in humans. *Anesth Analg.* 2003; 96(3):726–732. [PubMed: 12598253]
49. Mao J. Opioid-induced hyperalgesia. *Pain Clin Updates.* 2008; XVI(2):1–4.
50. Schulz S, Holtt V. Opioid withdrawal activates MAP kinase in locus coeruleus neurons in morphine-dependent rats in vivo. *Eur J Neurosci.* 1998; 10(3):1196–1201. [PubMed: 9753188]
51. Avidor-Reiss T, Nevo I, Saya D, Bayewitch M, Vogel Z. Opiate-induced adenylyl cyclase superactivation is isozyme-specific. *J Biol Chem.* 1997; 272(8):5040–5047. [PubMed: 9030567]
52. DeLeo JA, Tanga FY, Tawfik VL. Neuroimmune activation and neuroinflammation in chronic pain and opioid tolerance/hyperalgesia. *Neuroscientist.* 2004; 10(1):40–52. [PubMed: 14987447]
53. Ossipov MH, Lai J, King T, Vanderah TW, Porreca F. Underlying mechanisms of pronociceptive consequences of prolonged morphine exposure. *Biopolymers.* 2005; 80(2–3):319–324. [PubMed: 15795927]
54. Quartilho A, Mata HP, Ibrahim MM, et al. Production of paradoxical sensory hypersensitivity by alpha 2-adrenoreceptor agonists. *Anesthesiology.* 2004; 100(6):1538–1544. [PubMed: 15166576]
55. Gomes BA, Shen J, Stafford K, Patel M, Yoburn BC. Mu-opioid receptor downregulation and tolerance are not equally dependent upon G-protein signaling. *Pharmacol Biochem Behav.* 2002; 72(1–2):273–278. [PubMed: 11900797]
56. Fan XL, Zhang JS, Zhang XQ, Ma L. Chronic morphine treatment and withdrawal induce up-regulation of c-Jun N-terminal kinase 3 gene expression in rat brain. *Neuroscience.* 2003; 122(4):997–1002. [PubMed: 14643766]
57. Bohn LM, Lefkowitz RJ, Caron MG. Differential mechanisms of morphine antinociceptive tolerance revealed in (beta)arrestin-2 knock-out mice. *J Neurosci.* 2002; 22(23):10494–10500. [PubMed: 12451149]
58. Cox BM, Crowder AT. Receptor domains regulating mu opioid receptor uncoupling and internalization: relevance to opioid tolerance. *Mol Pharmacol.* 2004; 65(3):492–495. [PubMed: 14978226]
59. Heinzen EL, Pollack GM. Pharmacodynamics of morphine-induced neuronal nitric oxide production and antinociceptive tolerance development. *Brain Res.* 2004; 1023(2):175–184. [PubMed: 15374743]
60. Leck KJ, Bartlett SE, Smith MT, et al. Deletion of guanine nucleotide binding protein alpha z subunit in mice induces a gene dose dependent tolerance to morphine. *Neuropharmacology.* 2004; 46(6):836–846. [PubMed: 15033343]

61. Lim G, Wang S, Zeng Q, Sung B, Yang L, Mao J. Expression of spinal NMDA receptor and PKC γ after chronic morphine is regulated by spinal glucocorticoid receptor. *J Neurosci*. 2005; 25(48):11145–11154. [PubMed: 16319314]
62. Maldonado R, Blendy JA, Tzavara E, et al. Reduction of morphine abstinence in mice with a mutation in the gene encoding CREB. *Science*. 1996; 273(5275):657–659. [PubMed: 8662559]
63. Liang D, Li X, Clark JD. Increased expression of Ca²⁺/calmodulin-dependent protein kinase II α during chronic morphine exposure. *Neuroscience*. 2004; 123(3):769–775. [PubMed: 14706789]
64. McLaughlin JP, Myers LC, Zarek PE, et al. Prolonged kappa opioid receptor phosphorylation mediated by G-protein receptor kinase underlies sustained analgesic tolerance. *J Biol Chem*. 2004; 279(3):1810–1818. [PubMed: 14597630]
65. Zhang J, Ferguson SS, Barak LS, et al. Role for G protein-coupled receptor kinase in agonist-specific regulation of mu-opioid receptor responsiveness. *Proc Natl Acad Sci U S A*. 1998; 95(12):7157–7162. [PubMed: 9618555]
66. Thakker DR, Standifer KM. Induction of G protein-coupled receptor kinases 2 and 3 contributes to the cross-talk between mu and ORL1 receptors following prolonged agonist exposure. *Neuropharmacology*. 2002; 43(6):979–990. [PubMed: 12423667]
67. Eitan S, Bryant CD, Saliminejad N, et al. Brain region-specific mechanisms for acute morphine-induced mitogen-activated protein kinase modulation and distinct patterns of activation during analgesic tolerance and locomotor sensitization. *J Neurosci*. 2003; 23(23):8360–8369. [PubMed: 12967998]
68. Asensio VJ, Miralles A, Garcia-Sevilla JA. Stimulation of mitogen-activated protein kinase kinases (MEK1/2) by mu-, delta- and kappa-opioid receptor agonists in the rat brain: regulation by chronic morphine and opioid withdrawal. *Eur J Pharmacol*. 2006; 539(1–2):49–56. [PubMed: 16678156]
69. Moulédous L, Diaz MF, Gutstein HB. Extracellular signal-regulated kinase (ERK) inhibition does not prevent the development or expression of tolerance to and dependence on morphine in the mouse. *Pharmacol Biochem Behav*. 2007; 88(1):39–46. [PubMed: 17764731]
70. Rozenfeld R, Devi LA. Receptor heterodimerization leads to a switch in signaling: beta-arrestin2-mediated ERK activation by mu-delta opioid receptor heterodimers. *FASEB J*. 2007; 21(10):2455–2465. [PubMed: 17384143]
71. Bilecki W, Zapart G, Ligeza A, Wawrzczak-Bargiela A, Urbanski MJ, Przewlocki R. Regulation of the extracellular signal-regulated kinases following acute and chronic opioid treatment. *Cell Mol Life Sci*. 2005; 62(19–20):2369–2375. [PubMed: 16158186]
72. Narita M, Ioka M, Suzuki M, Suzuki T. Effect of repeated administration of morphine on the activity of extracellular signal regulated kinase in the mouse brain. *Neurosci Lett*. 2002; 324(2):97–100. [PubMed: 11988336]
73. Liu WT, Li HC, Song XS, Huang ZJ, Song XJ. EphB receptor signaling in mouse spinal cord contributes to physical dependence on morphine. *FASEB J*. 2009; 23(1):90–98. [PubMed: 18772347]
74. Chen Y, Geis C, Sommer C. Activation of TRPV1 contributes to morphine tolerance: involvement of the mitogen-activated protein kinase signaling pathway. *J Neurosci*. 2008; 28(22):5836–5845. [PubMed: 18509045]
75. Pareek TK, Kulkarni AB. Cdk5: a new player in pain signaling. *Cell Cycle*. 2006; 5(6):585–588. [PubMed: 16552189]
76. Callahan RJ, Au JD, Paul M, Liu C, Yost CS. Functional inhibition by methadone of *N*-methyl-D-aspartate receptors expressed in *Xenopus* oocytes: stereospecific and subunit effects. *Anesth Analg*. 2004; 98(3):653–659. table of contents. [PubMed: 14980914]
77. Díaz A, Flórez J, Pazos A, Hurlé MA. Opioid tolerance and supersensitivity induce regional changes in the autoradiographic density of dihydropyridine-sensitive calcium channels in the rat central nervous system. *Pain*. 2000; 86(3):227–235. [PubMed: 10812252]
78. McCleskey EW, Gold MS. Ion channels of nociception. *Annu Rev Physiol*. 1999; 61:835–856. [PubMed: 10099712]
79. Mitchell JM, Basbaum AI, Fields HL. A locus and mechanism of action for associative morphine tolerance. *Nat Neurosci*. 2000; 3(1):47–53. [PubMed: 10607394]

80. Liang DY, Clark JD. Modulation of the NO/CO-cGMP signaling cascade during chronic morphine exposure in mice. *Neurosci Lett*. 2004; 365(1):73–77. [PubMed: 15234476]
81. Polakiewicz RD, Schieferl SM, Gingras AC, Sonenberg N, Comb MJ. mu-Opioid receptor activates signaling pathways implicated in cell survival and translational control. *J Biol Chem*. 1998; 273(36):23534–23541. [PubMed: 9722592]
82. Mao J, Price DD, Lu J, Mayer DJ. Antinociceptive tolerance to the mu-opioid agonist DAMGO is dose-dependently reduced by MK-801 in rats. *Neurosci Lett*. 1998; 250(3):193–196. [PubMed: 9708865]
83. Vaughan CW, Ingram SL, Connor MA, Christie MJ. How opioids inhibit GABA-mediated neurotransmission. *Nature*. 1997; 390(6660):611–614. [PubMed: 9403690]
84. Ingram SL, Vaughan CW, Bagley EE, Connor M, Christie MJ. Enhanced opioid efficacy in opioid dependence is caused by an altered signal transduction pathway. *J Neurosci*. 1998; 18(24):10269–10276. [PubMed: 9852564]
85. Lu L, Huang M, Liu Z, Ma L. Cholecystokinin-B receptor antagonists attenuate morphine dependence and withdrawal in rats. *Neuroreport*. 2000; 11(4):829–832. [PubMed: 10757528]
86. Mao J. NMDA and opioid receptors: their interactions in antinociception, tolerance and neuroplasticity. *Brain Res Brain Res Rev*. 1999; 30(3):289–304. [PubMed: 10567729]
87. Liaw WJ, Zhang B, Tao F, Yaster M, Johns RA, Tao YX. Knockdown of spinal cord postsynaptic density protein-95 prevents the development of morphine tolerance in rats. *Neuroscience*. 2004; 123(1):11–15. [PubMed: 14667437]
88. Liu JG, Prather PL. Chronic agonist treatment converts antagonists into inverse agonists at delta-opioid receptors. *J Pharmacol Exp Ther*. 2002; 302(3):1070–1079. [PubMed: 12183665]
89. Davis AM, Inturrisi CE. D-Methadone blocks morphine tolerance and *N*-methyl-D-aspartate-induced hyperalgesia. *J Pharmacol Exp Ther*. 1999; 289(2):1048–1053. [PubMed: 10215686]
90. Langerman L, Zakowski MI, Piskoun B, Grant GJ. Hot plate versus tail flick: evaluation of acute tolerance to continuous morphine infusion in the rat model. *J Pharmacol Toxicol Methods*. 1995; 34(1):23–27. [PubMed: 7496043]
91. Hiltunen P, Raudaskoski T, Ebeling H, Moilanen I. Does pain relief during delivery decrease the risk of postnatal depression? *Acta Obstet Gynecol Scand*. 2004; 83(3):257–261. [PubMed: 14995921]
92. Crain SM, Shen KF. After chronic opioid exposure sensory neurons become supersensitive to the excitatory effects of opioid agonists and antagonists as occurs after acute elevation of GM1 ganglioside. *Brain Res*. 1992; 575(1):13–24. [PubMed: 1324084]
93. Grisel JE, Watkins LR, Maier SF. Associative and non-associative mechanisms of morphine analgesic tolerance are neurochemically distinct in the rat spinal cord. *Psychopharmacology*. 1996; 128(3):248–255. [PubMed: 8972544]
94. Laurent P, Becker JA, Valverde O, et al. The prolactin-releasing peptide antagonizes the opioid system through its receptor GPR10. *Nat Neurosci*. 2005; 8(12):1735–1741. [PubMed: 16299503]
95. Ueda H. Anti-opioid systems in morphine tolerance and addiction: locus-specific involvement of nociceptin and the NMDA receptor. *Novartis Found Symp*. 2004; 261:155–162. discussion 162–156, 191–153. [PubMed: 15469049]
96. McClean G. Cholecystokinin antagonists a new way to improve the analgesia from old analgesics? *Curr Pharm Des*. 2004; 10(3):303–314. [PubMed: 14754389]
97. Ueda H, Inoue M, Takeshima H, Iwasawa Y. Enhanced spinal nociceptin receptor expression develops morphine tolerance and dependence. *J Neurosci*. 2000; 20(20):7640–7647. [PubMed: 11027224]
98. Rothman RB. A review of the role of antiopioid peptides in morphine tolerance and dependence. *Synapse*. 1992; 12(2):129–138. [PubMed: 1362289]
99. Lötsch J, Flühr K, Neddermayer T, Doebering A, Geisslinger G. The consequence of concomitantly present functional genetic variants for the identification of functional genotype-phenotype associations in pain. *Clin Pharmacol Ther*. 2009; 85(1):25–30. [PubMed: 18548001]
100. Lötsch J, Geisslinger G. Relevance of frequent mu-opioid receptor polymorphisms for opioid activity in healthy volunteers. *Pharmacogenomics J*. 2006; 6(3):200–210. [PubMed: 16415919]

101. Lötsch J, Skarke C, Liefhold J, Geisslinger G. Genetic predictors of the clinical response to opioid analgesics: clinical utility and future perspectives. *Clin Pharmacokinet.* 2004; 43(14):983–1013. [PubMed: 15530129]
102. Oertel B, Lötsch J. Genetic mutations that prevent pain: implications for future pain medication. *Pharmacogenomics.* 2008; 9(2):179–194. [PubMed: 18370847]
103. Stamer UM, Stuber F. Genetic factors in pain and its treatment. *Curr Opin Anaesthesiol.* 2007; 20(5):478–484. [PubMed: 17873601]
104. Stamer UM, Stuber F. The pharmacogenetics of analgesia. *Expert Opin Pharmacother.* 2007; 8(14):2235–2245. [PubMed: 17927480]
105. Campa D, Gioia A, Tomei A, Poli P, Barale R. Association of *ABCB1/MDR1* and *OPRM1* gene polymorphisms with morphine pain relief. *Clin Pharmacol Ther.* 2008; 83(4):559–566. [PubMed: 17898703]
106. Shabalina SA, Zaykin DV, Gris P, et al. Expansion of the human mu-opioid receptor gene architecture: novel functional variants. *Hum Mol Genet.* 2009; 18(6):1037–1051. [PubMed: 19103668]
107. Diatchenko L, Nackley AG, Slade GD, et al. Catechol-*O*-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli. *Pain.* 2006; 125(3):216–224. [PubMed: 16837133]
108. Mukherjee N, Kidd KK, Pakstis AJ, et al. The complex global pattern of genetic variation and linkage disequilibrium at catechol-*O*-methyltransferase. *Mol Psychiatry.* 2010; 15(2):216. [PubMed: 18574484]
109. Mogil JS, Ritchie J, Smith SB, et al. Melanocortin-1 receptor gene variants affect pain and mu-opioid analgesia in mice and humans. *J Med Genet.* 2005; 42(7):583–587. [PubMed: 15994880]
110. Mogil JS, Wilson SG, Chesler EJ, et al. The melanocortin-1 receptor gene mediates female-specific mechanisms of analgesia in mice and humans. *Proc Natl Acad Sci U S A.* 2003; 100(8):4867–4872. [PubMed: 12663858]
111. Enggaard TP, Poulsen L, Arendt-Nielsen L, Brosen K, Ossig J, Sindrup SH. The analgesic effect of tramadol after intravenous injection in healthy volunteers in relation to *CYP2D6*. *Anesth Analg.* 2006; 102(1):146–150. [PubMed: 16368820]
112. Stamer UM, Lehnen K, Hothker F, et al. Impact of *CYP2D6* genotype on postoperative tramadol analgesia. *Pain.* 2003; 105(1–2):231–238. [PubMed: 14499440]
113. Stamer UM, Musshoff F, Kobilay M, Madea B, Hoeft A, Stuber F. Concentrations of tramadol and *O*-desmethyltramadol enantiomers in different *CYP2D6* genotypes. *Clin Pharmacol Ther.* 2007; 82(1):41–47. [PubMed: 17361124]
114. Stamer UM, Stuber F. Codeine and tramadol analgesic efficacy and respiratory effects are influenced by *CYP2D6* genotype. *Anaesthesia.* 2007; 62(12):1294–1295. author reply 1295–1296. [PubMed: 17991273]
115. Kirchheiner J, Keulen JT, Bauer S, Roots I, Brockmoller J. Effects of the *CYP2D6* gene duplication on the pharmacokinetics and pharmacodynamics of tramadol. *J Clin Psychopharmacol.* 2008; 28(1):78–83. [PubMed: 18204346]
116. Gan SH, Ismail R, Wan Adnan WA, Zulmi W. Impact of *CYP2D6* genetic polymorphism on tramadol pharmacokinetics and pharmacodynamics. *Mol Diagn Ther.* 2007; 11(3):171–181. [PubMed: 17570739]
117. Voronov P, Przybylo HJ, Jagannathan N. Apnea in a child after oral codeine: a genetic variant—an ultra-rapid metabolizer. *Paediatr Anaesth.* 2007; 17(7):684–687. [PubMed: 17564651]
118. Coulbault L, Beaussier M, Verstuyft C, et al. Environmental and genetic factors associated with morphine response in the postoperative period. *Clin Pharmacol Ther.* 2006; 79(4):316–324. [PubMed: 16580900]
119. Holthe M, Rakvag TN, Klestad P, et al. Sequence variations in the UDP-glucuronosyltransferase 2B7 (*UGT2B7*) gene: identification of 10 novel single nucleotide polymorphisms (SNPs) and analysis of their relevance to morphine glucuronidation in cancer patients [published correction appears in *Pharmacogenomics J.* 2003;3(4):248]. *Pharmacogenomics J.* 2003; 3(1):17–26. [PubMed: 12629580]

120. Innocenti F, Liu W, Fackenthal D, et al. Single nucleotide polymorphism discovery and functional assessment of variation in the UDP-glucuronosyltransferase 2B7 gene. *Pharmacogenet Genomics*. 2008; 18(8):683–697. [PubMed: 18622261]
121. Mehlotra RK, Bockarie MJ, Zimmerman PA. Prevalence of *UGT1A9* and *UGT2B7* nonsynonymous single nucleotide polymorphisms in West African, Papua New Guinean, and North American populations. *Eur J Clin Pharmacol*. 2007; 63(1):1–8. [PubMed: 17115150]
122. Blake MJ, Abdel-Rahman SM, Pearce RE, Leeder JS, Kearns GL. Effect of diet on the development of drug metabolism by cytochrome P-450 enzymes in healthy infants. *Pediatr Res*. 2006; 60(6):717–723. [PubMed: 17065585]
123. Blake MJ, Gaedigk A, Pearce RE, et al. Ontogeny of dextromethorphan *O*- and *N*-demethylation in the first year of life. *Clin Pharmacol Ther*. 2007; 81(4):510–516. [PubMed: 17301735]
124. Allegaert K, Anderson BJ, van den Anker JN, Vanhaesebrouck S, de Zegher F. Renal drug clearance in preterm neonates: relation to prenatal growth. *Ther Drug Monit*. 2007; 29(3):284–291. [PubMed: 17529884]
125. Anderson BJ, Allegaert K, Holford NH. Population clinical pharmacology of children: general principles. *Eur J Pediatr*. 2006; 165(11):741–746. [PubMed: 16807730]
126. Anderson BJ, Allegaert K, Holford NH. Population clinical pharmacology of children: modelling covariate effects. *Eur J Pediatr*. 2006; 165(12):819–829. [PubMed: 16807729]
127. Evans WE, McLeod HL. Pharmacogenomics: drug disposition, drug targets, and side effects. *N Engl J Med*. 2003; 348(6):538–549. [PubMed: 12571262]
128. Weinshilboum R. Inheritance and drug response. *N Engl J Med*. 2003; 348(6):529–537. [PubMed: 12571261]
129. Bond C, LaForge KS, Tian M, et al. Single-nucleotide polymorphism in the human mu opioid receptor gene alters beta-endorphin binding and activity: possible implications for opiate addiction. *Proc Natl Acad Sci U S A*. 1998; 95(16):9608–9613. [PubMed: 9689128]
130. Höllt V. A polymorphism (A118G) in the mu-opioid receptor gene affects the response to morphine-6-glucuronide in humans. *Pharmacogenetics*. 2002; 12(1):1–2. [PubMed: 11773858]
131. Lotsch J, Skarke C, Tegeder I, Geisslinger G. Drug interactions with patient-controlled analgesia. *Clin Pharmacokinet*. 2002; 41(1):31–57. [PubMed: 11825096]
132. Compton P, Geschwind DH, Alarcon M. Association between human mu-opioid receptor gene polymorphism, pain tolerance, and opioid addiction. *Am J Med Genet B Neuropsychiatr Genet*. 2003; 121B(1):76–82. [PubMed: 12898579]
133. Beyer A, Koch T, Schroder H, Schulz S, Hollt V. Effect of the A118G polymorphism on binding affinity, potency and agonist-mediated endocytosis, desensitization, and resensitization of the human mu-opioid receptor. *J Neurochem*. 2004; 89(3):553–560. [PubMed: 15086512]
134. Ross JR, Riley J, Taegetmeyer AB, et al. Genetic variation and response to morphine in cancer patients: catechol-*O*-methyltransferase and multidrug resistance-1 gene polymorphisms are associated with central side effects. *Cancer*. 2008; 112(6):1390–1403. [PubMed: 18257092]
135. Wager TD, Scott DJ, Zubieta JK. Placebo effects on human mu-opioid activity during pain. *Proc Natl Acad Sci U S A*. 2007; 104(26):11056–11061. [PubMed: 17578917]
136. Ribeiro SC, Kennedy SE, Smith YR, Stohler CS, Zubieta JK. Interface of physical and emotional stress regulation through the endogenous opioid system and mu-opioid receptors. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005; 29(8):1264–1280. [PubMed: 16256255]
137. Zubieta JK, Heitzeg MM, Smith YR, et al. COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. *Science*. 2003; 299(5610):1240–1243. [PubMed: 12595695]
138. Simons SH, Anand KJS. Pain control: opioid dosing, population kinetics and side-effects. *Semin Fetal Neonatal Med*. 2006; 11(4):260–267. [PubMed: 16621750]
139. Zubieta JK, Ketter TA, Bueller JA, et al. Regulation of human affective responses by anterior cingulate and limbic mu-opioid neurotransmission. *Arch Gen Psychiatry*. 2003; 60(11):1145–1153. [PubMed: 14609890]
140. Dewey WL. Various factors which affect the rate of development of tolerance and physical dependence to abused drugs. *NIDA Res Monogr*. 1984; 54:39–49. [PubMed: 6442762]

141. Hovav E, Weinstock M. Temporal factors influencing the development of acute tolerance to opiates. *J Pharmacol Exp Ther*. 1987; 242(1):251–256. [PubMed: 3612531]
142. Ceger P, Kuhn CM. Opiate withdrawal in the neonatal rat: relationship to duration of treatment and naloxone dose. *Psychopharmacology*. 2000; 150(3):253–259. [PubMed: 10923752]
143. Kissin I, Lee SS, Arthur GR, Bradley EL Jr. Effect of midazolam on development of acute tolerance to alfentanil: the role of pharmacokinetic interactions. *Anesth Analg*. 1997; 85(1):182–187. [PubMed: 9212144]
144. Anand KJS, McIntosh N, Lagercrantz H, Young TE, Vasa RK, Barton BA. Analgesia and sedation in ventilated preterm neonates: results from the pilot N.O.P.A.I.N. trial. *Arch Pediatr Adolesc Med*. 1999; 153(4):331–338. [PubMed: 10201714]
145. Thornton SR, Smith FL. Characterization of neonatal rat fentanyl tolerance and dependence. *J Pharmacol Exp Ther*. 1997; 281(1):514–521. [PubMed: 9103539]
146. Marshall H, Porteous C, McMillan I, MacPherson SG, Nimmo WS. Relief of pain by infusion of morphine after operation: does tolerance develop? *Br Med J (Clin Res Ed)*. 1985; 291(6487):19–21.
147. Bouwmeester NJ, Anand KJS, van Dijk M, Hop WC, Boomsma F, Tibboel D. Hormonal and metabolic stress responses after major surgery in children aged 0–3 years: a double-blind, randomized trial comparing the effects of continuous versus intermittent morphine. *Br J Anaesth*. 2001; 87(3):390–399. [PubMed: 11517122]
148. Bardo MT, Hughes RA. Single-dose tolerance to morphine-induced analgesic and hypoactive effects in infant rats. *Dev Psychobiol*. 1981; 14(5):415–423. [PubMed: 6268473]
149. Eaton DG, Wertheim D, Oozeer R, Royston P, Dubowitz L, Dubowitz V. The effect of pethidine on the neonatal EEG. *Dev Med Child Neurol*. 1992; 34(2):155–163. [PubMed: 1733821]
150. Franck LS, Miaskowski C. The use of intravenous opioids to provide analgesia in critically ill, premature neonates: a research critique. *J Pain Symptom Manage*. 1998; 15(1):41–69. [PubMed: 9436340]
151. Doberczak TM, Kandall SR, Wilets I. Neonatal opiate abstinence syndrome in term and preterm infants. *J Pediatr*. 1991; 118(6):933–937. [PubMed: 2040931]
152. Bhat R, Abu-Harb M, Chari G, Gulati A. Morphine metabolism in acutely ill preterm newborn infants. *J Pediatr*. 1992; 120(5):795–799. [PubMed: 1578319]
153. Hartley R, Quinn M, Green M, Levene MI. Morphine glucuronidation in premature neonates. *Br J Clin Pharmacol*. 1993; 35(3):314–317. [PubMed: 8471411]
154. Barrett DA, Barker DP, Rutter N, Pawula M, Shaw PN. Morphine, morphine-6-glucuronide and morphine-3-glucuronide pharmacokinetics in newborn infants receiving diamorphine infusions. *Br J Clin Pharmacol*. 1996; 41(6):531–537. [PubMed: 8799518]
155. Faura CC, Collins SL, Moore RA, McQuay HJ. Systematic review of factors affecting the ratios of morphine and its major metabolites. *Pain*. 1998; 74(1):43–53. [PubMed: 9514559]
156. Choe CH, Smith FL. Sedative tolerance accompanies tolerance to the analgesic effects of fentanyl in infant rats. *Pediatr Res*. 2000; 47(6):727–735. [PubMed: 10832729]
157. Craft RM, Stratmann JA, Bartok RE, Walpole TI, King SJ. Sex differences in development of morphine tolerance and dependence in the rat. *Psychopharmacology*. 1999; 143(1):1–7. [PubMed: 10227072]
158. Thornton SR, Wang AF, Smith FL. Characterization of neonatal rat morphine tolerance and dependence. *Eur J Pharmacol*. 1997; 340(2–3):161–167. [PubMed: 9537810]
159. Thornton SR, Smith FL. Long-term alterations in opiate antinociception resulting from infant fentanyl tolerance and dependence. *Eur J Pharmacol*. 1998; 363(2–3):113–119. [PubMed: 9881576]
160. Guinsburg R, de Araujo Peres C, Branco de Almeida MF, et al. Differences in pain expression between male and female newborn infants. *Pain*. 2000; 85(1–2):127–133. [PubMed: 10692611]
161. Bartocci M, Winberg J, Papendieck G, Mustica T, Serra G, Lagercrantz H. Cerebral hemodynamic response to unpleasant odors in the preterm newborn measured by near-infrared spectroscopy. *Pediatr Res*. 2001; 50(3):324–330. [PubMed: 11518818]
162. Bot G, Blake AD, Li S, Reisine T. Fentanyl and its analogs desensitize the cloned mu opioid receptor. *J Pharmacol Exp Ther*. 1998; 285(3):1207–1218. [PubMed: 9618424]

163. Gorman AL, Elliott KJ, Inturrisi CE. The D- and L-isomers of methadone bind to the non-competitive site on the *N*-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. *Neurosci Lett*. 1997; 223(1):5–8. [PubMed: 9058409]
164. Liu JG, Liao XP, Gong ZH, Qin BY. The difference between methadone and morphine in regulation of delta-opioid receptors underlies the antagonistic effect of methadone on morphine-mediated cellular actions. *Eur J Pharmacol*. 1999; 373(2–3):233–239. [PubMed: 10414444]
165. Ista E, van Dijk M, Gamel C, Tibboel D, de Hoog M. Withdrawal symptoms in children after long-term administration of sedatives and/or analgesics: a literature review. “Assessment remains troublesome”. *Intensive Care Med*. 2007; 33(8):1396–1406. [PubMed: 17541548]
166. Franck L, Vilardi J. Assessment and management of opioid withdrawal in ill neonates. *Neonatal Netw*. 1995; 14(2):39–48. [PubMed: 7746239]
167. Ista E, van Dijk M, Gamel C, Tibboel D, de Hoog M. Withdrawal symptoms in critically ill children after long-term administration of sedatives and/or analgesics: a first evaluation [published correction appears in *Neonatal Netw*. 1995;14(4):83]. *Crit Care Med*. 2008; 36(8):2427–2432. [PubMed: 18596622]
168. Finnegan LP. Effects of maternal opiate abuse on the newborn. *Fed Proc*. 1985; 44(7):2314–2317. [PubMed: 3884386]
169. Grünberger J, Linzmayer L, Fodor G, Presslich O, Praitner M, Loimer N. Static and dynamic pupillometry for determination of the course of gradual detoxification of opiate-addicted patients. *Eur Arch Psychiatry Clin Neurosci*. 1990; 240(2):109–112. [PubMed: 2149649]
170. Curley MA, Harris SK, Fraser KA, Johnson RA, Arnold JH. State Behavioral Scale: a sedation assessment instrument for infants and young children supported on mechanical ventilation. *Pediatr Crit Care Med*. 2006; 7(2):107–114. [PubMed: 16446601]
171. Cunliffe M, McArthur L, Dooley F. Managing sedation withdrawal in children who undergo prolonged PICU admission after discharge to the ward. *Paediatr Anaesth*. 2004; 14(4):293–298. [PubMed: 15078373]
172. Franck LS, Harris SK, Soetenga DJ, Amling JK, Curley MA. The Withdrawal Assessment Tool-1 (WAT-1): an assessment instrument for monitoring opioid and benzodiazepine withdrawal symptoms in pediatric patients. *Pediatr Crit Care Med*. 2008; 9(6):573–580. [PubMed: 18838937]
173. Bell RF. Low-dose subcutaneous ketamine infusion and morphine tolerance. *Pain*. 1999; 83(1):101–103. [PubMed: 10506678]
174. Tobias JD. Subcutaneous dexmedetomidine infusions to treat or prevent drug withdrawal in infants and children. *J Opioid Manag*. 2008; 4(4):187–191. [PubMed: 18837201]
175. Chana SK, Anand KJS. Can we use methadone for analgesia in neonates? *Arch Dis Child Fetal Neonatal Ed*. 2001; 85(2):F79–F81. [PubMed: 11517197]
176. Berde CB, Beyer JE, Bournaki MC, Levin CR, Sethna NF. Comparison of morphine and methadone for prevention of postoperative pain in 3- to 7-year-old children. *J Pediatr*. 1991; 119(1 pt 1):136–141. [PubMed: 2066846]
177. Berde CB, Sethna NF, Holzman RS, Reidy P, Gondek EJ. Pharmacokinetics of methadone in children and adolescents in the perioperative period. *Anesthesiology*. 1987; 67(3A):A519.
178. Gourlay GK, Wilson PR, Glynn CJ. Pharmacodynamics and pharmacokinetics of methadone during the perioperative period. *Anesthesiology*. 1982; 57(6):458–467. [PubMed: 6128949]
179. Liu JG, Liao XP, Gong ZH, Qin BY. Methadone-induced desensitization of the delta-opioid receptor is mediated by uncoupling of receptor from G protein. *Eur J Pharmacol*. 1999; 374(2):301–308. [PubMed: 10422772]
180. Lugo RA, MacLaren R, Cash J, Pribble CG, Vernon DD. Enteral methadone to expedite fentanyl discontinuation and prevent opioid abstinence syndrome in the PICU. *Pharmacotherapy*. 2001; 21(12):1566–1573. [PubMed: 11765307]
181. Williams PI, Sarginson RE, Ratcliffe JM. Use of methadone in the morphine-tolerant burned paediatric patient. *Br J Anaesth*. 1998; 80(1):92–95. [PubMed: 9505787]
182. Siddappa R, Fletcher JE, Heard AM, Kielma D, Cimino M, Heard CM. Methadone dosage for prevention of opioid withdrawal in children. *Paediatr Anaesth*. 2003; 13(9):805–810. [PubMed: 14617122]

183. Barrett DA, Simpson J, Rutter N, Kurihara-Bergstrom T, Shaw PN, Davis SS. The pharmacokinetics and physiological effects of buprenorphine infusion in premature neonates. *Br J Clin Pharmacol*. 1993; 36(3):215–219. [PubMed: 9114907]
184. Hamunen K, Olkkola KT, Maunuksela EL. Comparison of the ventilatory effects of morphine and buprenorphine in children. *Acta Anaesthesiol Scand*. 1993; 37(5):449–453. [PubMed: 8356856]
185. Maunuksela EL, Korpela R, Olkkola KT. Comparison of buprenorphine with morphine in the treatment of postoperative pain in children. *Anesth Analg*. 1988; 67(3):233–239. [PubMed: 3344976]
186. Maunuksela EL, Korpela R, Olkkola KT. Double-blind, multiple-dose comparison of buprenorphine and morphine in postoperative pain of children. *Br J Anaesth*. 1988; 60(1):48–55. [PubMed: 3337794]
187. Lehmann KA, Reichling U, Wirtz R. Influence of naloxone on the postoperative analgesic and respiratory effects of buprenorphine. *Eur J Clin Pharmacol*. 1988; 34(4):343–352. [PubMed: 3402520]
188. Olkkola KT, Hamunen K, Maunuksela EL. Clinical pharmacokinetics and pharmacodynamics of opioid analgesics in infants and children. *Clin Pharmacokinet*. 1995; 28(5):385–404. [PubMed: 7614777]
189. Johnson RE, Chutuape MA, Strain EC, Walsh SL, Stitzer ML, Bigelow GE. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *N Engl J Med*. 2000; 343(18):1290–1297. [PubMed: 11058673]
190. Robinson SE. Buprenorphine: an analgesic with an expanding role in the treatment of opioid addiction. *CNS Drug Rev*. 2002; 8(4):377–390. [PubMed: 12481193]
191. O'Connor PG. Treating opioid dependence: new data and new opportunities. *N Engl J Med*. 2000; 343(18):1332–1334. [PubMed: 11058680]
192. Gowing L, Ali R, White J. Buprenorphine for the management of opioid withdrawal. *Cochrane Database Syst Rev*. 2000; (3):CD002025. [PubMed: 10908521]
193. Kayemba-Kay's S, Laclede JP. Buprenorphine withdrawal syndrome in newborns: a report of 13 cases. *Addiction*. 2003; 98(11):1599–1604. [PubMed: 14616186]
194. Marquet P, Chevrel J, Lavignasse P, Merle L, Lachatre G. Buprenorphine withdrawal syndrome in a newborn. *Clin Pharmacol Ther*. 1997; 62(5):569–571. [PubMed: 9390114]
195. Hervé F, Quenum S. Buprenorphine (Subutex) and neonatal withdrawal syndrome [in French]. *Arch Pediatr*. 1998; 5(2):206–207. [PubMed: 10223149]
196. Lacroix I, Berrebi A, Chaumerliac C, Lapeyre-Mestre M, Montastruc JL, Damase-Michel C. Buprenorphine in pregnant opioid-dependent women: first results of a prospective study. *Addiction*. 2004; 99(2):209–214. [PubMed: 14756713]
197. McClain BC, Probst LA, Pinter E, Hartmannsgruber M. Intravenous clonidine use in a neonate experiencing opioid-induced myoclonus. *Anesthesiology*. 2001; 95(2):549–550. [PubMed: 11506132]
198. Hoder EL, Leckman JF, Ehrenkranz R, Kleber H, Cohen DJ, Poulsen JA. Clonidine in neonatal narcotic-abstinence syndrome. *N Engl J Med*. 1981; 305(21):1284. [PubMed: 7290147]
199. Hoder EL, Leckman JF, Poulsen J, et al. Clonidine treatment of neonatal narcotic abstinence syndrome. *Psychiatry Res*. 1984; 13(3):243–251. [PubMed: 6597462]
200. Kosten TR, Rounsaville BJ, Kleber HD. Comparison of clinician ratings to self reports of withdrawal during clonidine detoxification of opiate addicts. *Am J Drug Alcohol Abuse*. 1985; 11(1–2):1–10. [PubMed: 3904410]
201. Gold MS, Pottash AL, Extein I, Finn LB, Kleber HD. Clonidine in opiate withdrawal. *Curr Psychiatr Ther*. 1981; 20:285–291. [PubMed: 7326972]
202. Gold MS, Pottash AC, Sweeney DR, Kleber HD. Opiate withdrawal using clonidine: a safe, effective, and rapid nonopiate treatment. *JAMA*. 1980; 243(4):343–346. [PubMed: 7351747]
203. Honey BL, Benefield RJ, Miller JL, Johnson PN. α_2 -receptor agonists for treatment and prevention of iatrogenic opioid abstinence syndrome in critically ill patients. *Ann Pharmacother*. 2009; 43(9):1506–1511. [PubMed: 19690220]
204. Farag E, Chahlavi A, Argalious M, Ebrahim Z, Hill R, Bourdakos D, et al. Using dexmedetomidine to manage patients with cocaine and opioid withdrawal, who are undergoing

- cerebral angioplasty for cerebral vasospasm. *Anesth Analg.* 2006; 103(6):1618–1620. [PubMed: 17122286]
205. Multz AS. Prolonged dexmedetomidine infusion as an adjunct in treating sedation-induced withdrawal. *Anesth Analg.* 2003; 96(4):1054–1055. table of contents. [PubMed: 12651659]
 206. Finkel JC, Elrefai A. The use of dexmedetomidine to facilitate opioid and benzodiazepine detoxification in an infant. *Anesth Analg.* 2004; 98(6):1658–1659. [PubMed: 15155322]
 207. Finkel JC, Johnson YJ, Quezado ZM. The use of dexmedetomidine to facilitate acute discontinuation of opioids after cardiac transplantation in children. *Crit Care Med.* 2005; 33(9): 2110–2112. [PubMed: 16148487]
 208. Tobias JD. Dexmedetomidine to treat opioid withdrawal in infants following prolonged sedation in the pediatric ICU. *J Opioid Manag.* 2006; 2(4):201–205. [PubMed: 17319480]
 209. Phan H, Nahata MC. Clinical uses of dexmedetomidine in pediatric patients. *Paediatr Drugs.* 2008; 10(1):49–69. [PubMed: 18162008]
 210. Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch Neurol.* 2003; 60(11):1524–1534. [PubMed: 14623723]
 211. Backonja MM. Use of anticonvulsants for treatment of neuropathic pain. *Neurology.* 2002; 59(5 suppl 2):S14–17. [PubMed: 12221151]
 212. Freye E, Levy JV, Partecke L. Use of gabapentin for attenuation of symptoms following rapid opiate detoxification (ROD): correlation with neurophysiological parameters. *Neurophysiol Clin.* 2004; 34(2):81–89. [PubMed: 15130554]
 213. Kumar P, Jain MK. Gabapentin in the management of pentazocine dependence: a potent analgesic-anticraving agent. *J Assoc Physicians India.* 2003; 51:673–676. [PubMed: 14621035]
 214. Andrews N, Loomis S, Blake R, Ferrigan L, Singh L, McKnight AT. Effect of gabapentin-like compounds on development and maintenance of morphine-induced conditioned place preference. *Psychopharmacology (Berl).* 2001; 157(4):381–387. [PubMed: 11605097]
 215. Gustorff B, Kozek-Langenecker S, Kress HG. Gabapentin: the first preemptive antihyperalgesic for opioid withdrawal hyperalgesia? *Anesthesiology.* 2003; 98(6):1520–1521. [PubMed: 12766674]
 216. Sheridan RL, Keaney T, Stoddard F, Enfant R, Kadillack P, Breault L. Short-term propofol infusion as an adjunct to extubation in burned children. *J Burn Care Rehabil.* 2003; 24(6):356–360. [PubMed: 14610418]
 217. Feng JQ, Kendig JJ. Propofol potentiates the depressant effect of alfentanil in isolated neonatal rat spinal cord and blocks naloxone-precipitated hyperresponsiveness. *Neurosci Lett.* 1997; 229(1): 9–12. [PubMed: 9224789]
 218. Hasday JD, Weintraub M. Propoxyphene in children with iatrogenic morphine dependence. *Am J Dis Child.* 1983; 137(8):745–748. [PubMed: 6869331]
 219. Udkow G, Weintraub M. Use of propoxyphene napsylate for detoxification of a child with morphine sulfate tolerance and physical dependence. *J Pediatr.* 1978; 92(5):829–831. [PubMed: 25316]
 220. Neil A, Terenius L. D-Propoxyphene acts differently from morphine on opioid receptor-effector mechanisms. *Eur J Pharmacol.* 1981; 69(1):33–39. [PubMed: 6258941]
 221. Bisaga A, Comer SD, Ward AS, Popik P, Kleber HD, Fischman MW. The NMDA antagonist memantine attenuates the expression of opioid physical dependence in humans. *Psychopharmacology (Berl).* 2001; 157(1):1–10. [PubMed: 11512037]
 222. Maldonado C, Cauli O, Rodriguez-Arias M, Aguilar MA, Minarro J. Memantine presents different effects from MK-801 in motivational and physical signs of morphine withdrawal. *Behav Brain Res.* 2003; 144(1–2):25–35. [PubMed: 12946592]
 223. Popik P, Kozela E. Clinically available NMDA antagonist, memantine, attenuates tolerance to analgesic effects of morphine in a mouse tail flick test. *Pol J Pharmacol.* 1999; 51(3):223–231. [PubMed: 10600036]
 224. Unal CB, Owen MD, Millington WR. Cyclo(Gly-Gln) inhibits the cardiorespiratory depression produced by betaendorphin and morphine. *Brain Res.* 1997; 747(1):52–59. [PubMed: 9042527]

225. Owen MD, Gurun S, Zaloga GP, Millington WR. Glycyl-L-glutamine [beta-endorphin-(30–31)] attenuates hemorrhagic hypotension in conscious rats. *Am J Physiol*. 1997; 273(5 pt 2):R1598–R1606. [PubMed: 9374799]
226. Unal CB, Owen MD, Millington WR. Beta-endorphin-induced cardiorespiratory depression is inhibited by glycyl-L-glutamine, a dipeptide derived from beta-endorphin processing. *J Pharmacol Exp Ther*. 1994; 271(2):952–958. [PubMed: 7965817]
227. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med*. 2000; 342(20):1471–1477. [PubMed: 10816184]
228. Brook AD, Ahrens TS, Schaiff R, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med*. 1999; 27(12):2609–2615. [PubMed: 10628598]
229. Mercadante S. Opioid rotation for cancer pain: rationale and clinical aspects. *Cancer*. 1999; 86(9):1856–1866. [PubMed: 10547561]
230. Moryl N, Santiago-Palma J, Kornick C, et al. Pitfalls of opioid rotation: substituting another opioid for methadone in patients with cancer pain. *Pain*. 2002; 96(3):325–328. [PubMed: 11973005]
231. Haberkern CM, Lynn AM, Geiduschek JM, et al. Epidural and intravenous bolus morphine for postoperative analgesia in infants. *Can J Anaesth*. 1996; 43(12):1203–1210. [PubMed: 8955967]
232. Malviya S, Pandit UA, Merkel S, et al. A comparison of continuous epidural infusion and intermittent intravenous bolus doses of morphine in children undergoing selective dorsal rhizotomy. *Reg Anesth Pain Med*. 1999; 24(5):438–443. [PubMed: 10499756]
233. Henneberg SW, Hole P, Madsen de Haas I, Jensen PJ. Epidural morphine for postoperative pain relief in children. *Acta Anaesthesiol Scand*. 1993; 37(7):664–667. [PubMed: 8249555]
234. McCrory C, Diviney D, Moriarty J, Luke D, Fitzgerald D. Comparison between repeat bolus intrathecal morphine and an epidurally delivered bupivacaine and fentanyl combination in the management of post-thoracotomy pain with or without cyclooxygenase inhibition. *J Cardiothorac Vasc Anesth*. 2002; 16(5):607–611. [PubMed: 12407615]
235. Yaster M, Tobin JR, Billett C, Casella JF, Dover G. Epidural analgesia in the management of severe vaso-occlusive sickle cell crisis. *Pediatrics*. 1994; 93(2):310–315. [PubMed: 8121746]
236. Curley MAQ, Amling J, Gedeit RG, et al. Sedation management in pediatric patients supported on mechanical ventilation. *Pediatr Crit Care Med*. 2007; 8(3 suppl):A106.
237. Curley MAQ, Dodson BL, Arnold JH. Designing a nurse-implemented sedation algorithm for use in a pediatric intensive care unit: a preliminary report. *Pediatr Crit Care Med*. 2003; 4(3 suppl):A158.
238. Sury MR, Hatch DJ, Deeley T, Dicks-Mireaux C, Chong WK. Development of a nurse-led sedation service for paediatric magnetic resonance imaging. *Lancet*. 1999; 353(9165):1667–1671. [PubMed: 10335787]
239. Hammer GB, Ramamoorthy C, Cao H, et al. Postoperative analgesia after spinal blockade in infants and children undergoing cardiac surgery. *Anesth Analg*. 2005; 100(5):1283–1288. [PubMed: 15845670]
240. Atangana R, Ngowe Ngowe M, Binam F, Sosso MA. Morphine versus morphine-ketamine association in the management of post operative pain in thoracic surgery. *Acta Anaesthesiol Belg*. 2007; 58(2):125–127. [PubMed: 17710901]
241. Bossard AE, Guirimand F, Fletcher D, Gaude-Joindreau V, Chauvin M, Bouhassira D. Interaction of a combination of morphine and ketamine on the nociceptive flexion reflex in human volunteers. *Pain*. 2002; 98(1–2):47–57. [PubMed: 12098616]
242. Lauretti GR, Lima IC, Reis MP, Prado WA, Pereira NL. Oral ketamine and transdermal nitroglycerin as analgesic adjuvants to oral morphine therapy for cancer pain management. *Anesthesiology*. 1999; 90(6):1528–1533. [PubMed: 10360847]
243. Huang C, Long H, Shi YS, Han JS, Wan Y. Ketamine enhances the efficacy to and delays the development of tolerance to electroacupuncture-induced antinociception in rats. *Neurosci Lett*. 2005; 375(2):138–142. [PubMed: 15670657]

244. Shimoyama N, Shimoyama M, Inturrisi CE, Elliott KJ. Ketamine attenuates and reverses morphine tolerance in rodents. *Anesthesiology*. 1996; 85(6):1357–1366. [PubMed: 8968183]
245. Levine JD, Gordon NC, Taiwo YO,Coderre TJ. Potentiation of pentazocine analgesia by low-dose naloxone. *J Clin Invest*. 1988; 82(5):1574–1577. [PubMed: 3183054]
246. Cepeda MS, Africano JM, Manrique AM, Fragoso W, Carr DB. The combination of low dose of naloxone and morphine in PCA does not decrease opioid requirements in the postoperative period. *Pain*. 2002; 96(1–2):73–79. [PubMed: 11932063]
247. Cheung CLS, van Dijk M, Green JG, Tibboel D, Anand KJS. Effect of low-dose naloxone infusions on opioid tolerance in pediatric patients: a case-control study. *Intensive Care Med*. 2007; 33(1):190–194. [PubMed: 17089146]
248. Darnell, CM.; Thompson, J.; Stromberg, D.; Roy, L.; Sheeran, P. Effect of low-dose naloxone infusion on fentanyl requirements in critically ill children. *Pediatrics*. 2008. Available at: www.pediatrics.org/cgi/content/full/121/5/e1363
249. Andersen S, Dickenson AH, Kohn M, Reeve A, Rahman W, Ebert B. The opioid ketobemidone has a NMDA blocking effect. *Pain*. 1996; 67(2–3):369–374. [PubMed: 8951931]
250. Ebert B, Thorkildsen C, Andersen S, Christrup LL, Hjeds H. Opioid analgesics as non-competitive *N*-methyl-D-aspartate (NMDA) antagonists. *Biochem Pharmacol*. 1998; 56(5):553–559. [PubMed: 9783723]
251. Highfield DA, Grant S. *Ng*-nitro-L-arginine, an NOS inhibitor, reduces tolerance to morphine in the rat locus coeruleus. *Synapse*. 1998; 29(3):233–239. [PubMed: 9635893]
252. Lue WM, Su MT, Lin WB, Tao PL. The role of nitric oxide in the development of morphine tolerance in rat hippocampal slices. *Eur J Pharmacol*. 1999; 383(2):129–135. [PubMed: 10585526]
253. Vaupel DB, Kimes AS, London ED. Nitric oxide synthase inhibitors: preclinical studies of potential use for treatment of opioid withdrawal. *Neuropsychopharmacology*. 1995; 13(4):315–322. [PubMed: 8747756]
254. Vaupel DB, Kimes AS, London ED. Comparison of 7-nitroindazole with other nitric oxide synthase inhibitors as attenuators of opioid withdrawal. *Psychopharmacology (Berl)*. 1995; 118(4):361–368. [PubMed: 7568621]
255. Singh VP, Jain NK, Kulkarni SK. Fluoxetine suppresses morphine tolerance and dependence: modulation of NO-cGMP/DA/serotonergic pathways. *Methods Find Exp Clin Pharmacol*. 2003; 25(4):273–280. [PubMed: 12808472]
256. Tobias JD. Sedation and analgesia in the pediatric intensive care unit. *Pediatr Ann*. 2005; 34(8):636–645. [PubMed: 16149752]
257. Tobias JD. Sedation and analgesia in paediatric intensive care units: a guide to drug selection and use. *Paediatr Drugs*. 1999; 1(2):109–126. [PubMed: 10937446]

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.

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.

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; PLA₂, phospholipase A₂; δ -OR, δ opioid receptor; NO, nitric oxide; nNOS, neuronal nitric oxide synthetase; HPETE, hydroperoxyeicosatetraenoic acid.

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

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
Remifentanyl	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 McGraw-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

SNPs That Affect Opioid Analgesia/Tolerance

TABLE 4

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
<i>OPRM1</i> (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		
	IVS2-69[C→G intron 2	44.5	No effect		
<i>COMT</i> (catechol-O-methyl transferase)	472G→A exon 4	46.2	Morphine, M6G, fentanyl	0.67 ^d	105–107
<i>MC1R</i> (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			
<i>CYP2D6</i> (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)	
<i>ABCB1</i> (P glycoprotein)	3435C→T exon 1	47.6	Morphine	<<1 (less nausea)	117
	2677 G→T/A exon 3	2			
<i>UGT2B7</i> (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			

^aThe 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.

^bA 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.

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.