



# Prevention and Management of Procedural Pain in the Neonate: An Update

COMMITTEE ON FETUS AND NEWBORN and SECTION ON ANESTHESIOLOGY AND PAIN MEDICINE

The prevention of pain in neonates should be the goal of all pediatricians and health care professionals who work with neonates, not only because it is ethical but also because repeated painful exposures have the potential for deleterious consequences. Neonates at greatest risk of neurodevelopmental impairment as a result of preterm birth (ie, the smallest and sickest) are also those most likely to be exposed to the greatest number of painful stimuli in the NICU. Although there are major gaps in knowledge regarding the most effective way to prevent and relieve pain in neonates, proven and safe therapies are currently underused for routine minor, yet painful procedures. Therefore, every health care facility caring for neonates should implement (1) a pain-prevention program that includes strategies for minimizing the number of painful procedures performed and (2) a pain assessment and management plan that includes routine assessment of pain, pharmacologic and nonpharmacologic therapies for the prevention of pain associated with routine minor procedures, and measures for minimizing pain associated with surgery and other major procedures.

Previous guidance from the American Academy of Pediatrics (AAP) and the Canadian Pediatric Society addressed the need to assess neonatal pain, especially during and after diagnostic and therapeutic procedures.<sup>1,2</sup> These organizations also provided recommendations on preventing or minimizing pain in newborn infants and treating unavoidable pain promptly and adequately.<sup>1,2</sup> This statement updates previous recommendations with new evidence on the prevention, assessment, and treatment of neonatal procedural pain.

## BACKGROUND

Neonates are frequently subjected to painful procedures, with the most immature infants receiving the highest number of painful events.<sup>3-5</sup>

## abstract

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Despite recommendations from the AAP and other experts, neonatal pain continues to be inconsistently assessed and inadequately managed.<sup>2,3</sup> A large prospective study from France in 2008 found that specific pharmacologic or nonpharmacologic analgesia was given before painful procedures in only 21% of infants, and ongoing analgesia was given in an additional 34%.<sup>3</sup> Thus, infants received analgesia for approximately half of the procedures performed, with wide variation among facilities.

The prevention and alleviation of pain in neonates, particularly preterm infants, is important not only because it is ethical but also because exposure to repeated painful stimuli early in life is known to have short- and long-term adverse sequelae. These sequelae include physiologic instability, altered brain development, and abnormal neurodevelopment, somatosensory, and stress response systems, which can persist into childhood.<sup>5-15</sup> Nociceptive pathways are active and functional as early as 25 weeks' gestation and may elicit a generalized or exaggerated response to noxious stimuli in immature newborn infants.<sup>16</sup>

Researchers have demonstrated that a procedure-related painful stimulus that results in increased excitability of nociceptive neurons in the dorsal horn of the spinal cord accentuates the infant's sensitivity to subsequent noxious and nonnoxious sensory stimuli (ie, sensitization).<sup>17,18</sup> This persistent sensory hypersensitivity can be physiologically stressful, particularly in preterm infants.<sup>19-22</sup> Investigators have demonstrated increased stress-related markers and elevated free radicals after even simple procedures, such as routine heel punctures or tape removal from central venous catheters,<sup>23,24</sup> which can adversely affect future pain perception.<sup>8</sup> Specific cortical pain processing occurs even in preterm

infants; however, multiple factors interact to influence the nociceptive processing and/or behavioral responses to pain.<sup>14,16,25-27</sup> Noxious stimuli activate these signaling pathways but also activate the central inhibitory circuits, thus altering the balance between the excitatory and inhibitory feedback mechanisms. The immaturity of the dorsal horn synaptic connectivity and descending inhibitory circuits in neonates results in poor localization and discrimination of sensory input and poor noxious inhibitory modulation, thus facilitating central nervous system sensitization to repeated noxious stimuli.<sup>25</sup>

#### **ASSESSMENT OF PAIN AND STRESS IN THE NEONATE**

Reliable neonatal pain assessment tools are essential for the rating and management of neonatal pain, and their use has been strongly recommended by the AAP and by international researchers, including the International Evidence-Based Group for Neonatal Pain.<sup>1,2,28</sup> However, the effective management of pain in the neonate remains problematic because of the inability of the infant to report his or her own pain and the challenges of assessing pain in extremely premature, ill, and neurologically compromised neonates.<sup>29</sup> Thus, pain assessment tools reflect surrogate measures of physiologic and behavioral responses to pain. Although numerous neonatal pain scales exist (Table 1), only 5 pain scales have been subjected to rigorous psychometric testing with the patients serving as their own controls, measuring their physiologic and behavioral responses by using the scale in question (Neonatal Facial Coding System,<sup>30,31</sup> Premature Infant Pain Profile [PIPP],<sup>32-34</sup> Neonatal Pain and Sedation Scale,<sup>35,36</sup> Behavioral Infant Pain Profile,<sup>37</sup> and Douleur Aiguë du Nouveau-né<sup>38</sup>). Many of the current pain assessment tools have been tested against

existing or newly developed tools and against each other to determine which is more reliable for a particular population and application, but more research is needed.<sup>29,39</sup>

Contextual factors such as gestational age and behavioral state may play a significant role in pain assessment and are beginning to be included in some assessment tools (eg, the PIPP-Revised).<sup>40,41</sup> New and emerging technologies to measure pain responses, such as near-infrared spectroscopy, amplitude-integrated electroencephalography, functional MRI, skin conductance, and heart rate variability assessment, are being investigated.<sup>53,54</sup> These innovations hold promise in the development of neurophysiologically based methods for assessing noxious stimuli processing at the cortical level in neonates while they are awake, sedated, or anesthetized. If the neurophysiologic measures prove to be reliable and quantifiable, these measures could be used in the future to simultaneously correlate with the physiologic and behavioral pain assessment scales to determine the most clinically useful tool(s).

Many of the tools developed to measure acute pain in neonates are multidimensional in nature and include a combination of physiologic and behavioral signs. These tools were most commonly developed to assess unventilated infants; only a few scales are validated to assess pain in infants who are ventilated through an endotracheal tube or receiving nasal continuous positive airway pressure.<sup>42,55</sup> Recently, investigators reported that 2 behaviorally based, one-dimensional pain assessment tools (the Behavioral Indicators of Infant Pain and the Neonatal Facial Coding System) were more sensitive in detecting behavioral cues related to pain in term neonates than the PIPP.<sup>56</sup>

It is unlikely that a single, comprehensive pain assessment

**TABLE 1** Pain Assessment Tools for Neonates

Pain Assessment Tool	Number and GA of Infants Studied	Indicators	Intervention Studied	Validation Methodology	Intended Use
Neonatal Facial Coding System (NFCS) <sup>30,31</sup> (1998, 2003)	N = 40 24–32 wk GA 5–56 DOL	Brow lowering Eye squeeze Nasolabial furrowing Lip opening Vertical mouth stretch Horizontal mouth stretch Taut tongue Chin quiver Lip pursing GA Behavioral state Maximum HR % Decrease in O <sub>2</sub> sat Brow bulge Eye squeeze Nasolabial furrow Crying Behavioral state Facial expressions Extremities/tone	Postoperative abdominal or thoracic surgery	Patients served as controls Interrater reliability: 0.86 Construct validity: demonstrated Feasibility: established	Acute pain Prolonged pain Postoperative pain
Premature Infant Pain Profile (PIPP) <sup>32–34</sup> (1996, 1999)	N = 211, 43, 24 Age: 28–40 wk GA	Vital signs (HR, BP, RR, O <sub>2</sub> sat)	Heel lance	Patients served as controls Internal consistency: 0.71 Construct validity: established Interrater reliability: 0.93–0.96 Intrater reliability: 0.94–0.98	Acute pain
Neonatal Pain Agitation and Sedation Scale (NPASS) <sup>35,36</sup> (2010) ( <a href="http://www.n-pass.com/research.html">http://www.n-pass.com/research.html</a> )	N = 42 Age: 23–40 wk GA 1–100 DOL	Behavioral state Facial expressions Extremities/tone	Heel lance	Validated against PIPP Interrater reliability: 0.86–0.93 Internal consistency: 0.84–0.89 Construct (discriminate) validity: established Convergent validity: correlation with the PIPP scores Spearman rank correlation coefficient of 0.75 and 0.72 Test-retest reliability: 0.87	Acute pain Prolonged pain Level of sedation
Behavioral Indicators of Infant Pain (BIIP) <sup>37</sup> (2007)	N = 92 Age: 24–32 wk GA	Behavioral state Facial expressions Hand movements	Heel lance	Validated against NIPS Internal consistency: 0.82 Interrater reliability: 0.80–0.92 Construct validity: 85.9 Concurrent validity: correlations between the BIIP and NIPS = 0.64. Correlations between the BIIP and mean HR also remained moderate between GAs: earlier born = 0.33, <i>P</i> < .05; later born, <i>r</i> = 0.50, <i>P</i> < .001	Acute pain
Douleur Aiguë du Nouveau-né (DAN) <sup>38</sup> (1997)	N = 42 Age: 24–41 wk GA	Facial movements Limb movements Vocal expression Maximum HR % Decrease in O <sub>2</sub> sat Brow bulge Eye squeeze Nasolabial furrow GA and behavioral state assessed if pain response detected	Heel lance Venipuncture	Patients served as controls Internal consistency: 0.88 Interrater reliability: 91.2 (Krippendorff)	Procedural pain
Premature Infant Pain Profile—Revised (PIPP-R) <sup>40,41</sup> (2014)	N = 52, 85, 31 Age: 25–40 wk GA	Maximum HR % Decrease in O <sub>2</sub> sat Brow bulge Eye squeeze Nasolabial furrow GA and behavioral state assessed if pain response detected	Retrospective comparison of PIPP and PIPP-R scores	Validated against PIPP Construct validity: established Feasibility: established	Acute pain

**TABLE 1** Continued

Pain Assessment Tool	Number and GA of Infants Studied	Indicators	Intervention Studied	Validation Methodology	Intended Use
Faceless Acute Neonatal Pain Scale (FANS) <sup>42</sup> (2010)	N = 53 Age: 30–35 wk GA	HR change Acute discomfort (bradycardia, desat) Limb movements Vocal expression (must be nonintubated) Facial expression Crying	Heel lance	Validated against DAN Interrater reliability: 0.92 (0.9–0.98)  Internal consistency: Cronbach's $\alpha$ = 0.72 The ICC between the FANS and DAN scores was 0.88 (0.76–0.93) Validated against VAS Concurrent validity: correlations with VAS ranged from 0.53 to 0.84. Intrater reliability: 0.92–0.97 Internal consistency: Cronbach's $\alpha$ 's were 0.95, 0.87, and 0.88 for before, during, and after the procedures, respectively Validated against the Objective Pain Score Interrater reliability: 0.72 Construct validity: yes Discriminant validity: yes	Acute pain Developed for use when the neonate's face is not completely visible related to respiratory devices  Acute pain Postoperative pain
Neonatal Infant Pain Scale (NIPS) <sup>43</sup> (1993)	N = 38 Age: 26–47 wk GA	Breathing patterns Arm movements Leg movements State of arousal Crying Requires O <sub>2</sub> to maintain sat at 95% Increased blood pressure, HR Expression Sleep state Alertness	Needle insertion  Postoperative pain	Validated against Numeric Rating Scale  Internal consistency: Cronbach's $\alpha$ = 0.88 for nonventilated, 0.84 for ventilated patients Interrater reliability: 0.79	Persistent or prolonged pain Level of sedation
Crying Requires Increased oxygen administration, Increased vital signs, Expression, Sleeplessness (CRIS) <sup>44</sup> (1995)	N = 24 Age: 32–60 wk GA 1382 observations	Respiratory response in ventilated patient Crying in spontaneously breathing patient	Tertiary NICU care, including ventilation	Concurrent validity: Pearson product-moment correlation coefficient between COMFORTneo and NRS-pain = 0.54 Correlation coefficient: 0.75 (95% confidence interval: 0.70–0.79; $P$ < .0001)	
COMFORTneo <sup>45</sup> (2009)	N = 286 Age: 24.6–42.6 wk GA  3600 assessments	Body movement Facial tension Body muscle tone Crying	Heel lance	Validated different GAS against CRIES, NIPS, and PIPP Concurrent validity: premature infants PIPP versus COVERS, $r$ = 0.84; full-term infants NIPS versus COVERS, $r$ = 0.95 Construct validity: baseline ( $P$ < .05); heel stick ( $P$ < .05); recovery ( $P$ < .05)	Acute pain
COVERS Neonatal pain scale <sup>46</sup> (2010)	N = 21 Age: 27–40 wk GA	F <sub>102</sub> requirement  Vital signs (HR, BP, frequency of apnea/bradycardia Facial expression Resting state Body movements			

**TABLE 1** Continued

Pain Assessment Tool	Number and GA of Infants Studied	Indicators	Intervention Studied	Validation Methodology	Intended Use
Pain Assessment in Neonates (PAIN) <sup>47</sup> (2002)	<i>N</i> = 196 neonates Age: 26–47 wk GA	Facial expression Cry Breathing pattern Extremity movement State of arousal FiO <sub>2</sub> required for sat >95% Increase in HR Posture/tone Cry Sleep pattern Expression Color Respirations HR O <sub>2</sub> sat BP Nurse's perception	Heel lance, suctioning, IV placement, circumcision, NG tube insertion, tape or IV removal	Adapted from NIPS and CRIES Inter-rater reliability: not established Correlation between the total scores on the two scales (NIPS and PAIN) was 0.93 ( <i>P</i> < .001).	Acute pain
Pain Assessment Tool (PAT) <sup>48,49</sup> (2005)	<i>N</i> = 144 Age: 27–40 wk GA	CNS state Breathing Movement Tone Face HR changes Mean BP changes Facial activity Body movements Quality of sleep Quality of contact with nurses Consolability Alertness Duration of crying	Ventilated and postoperative neonates	Validated against CRIES and VAS Interrater reliability: 0.85 Correlation between PAT and CRIES scores ( <i>r</i> = 0.76) and (0.38) between the PAT score and VAS	Prolonged pain
Scale for Use in Newborns (SUN) <sup>50</sup> (1998)	<i>N</i> = 33 Age: 24–40 wk GA 0–214 DOL 68 procedures	CNS state Breathing Movement Tone Face HR changes Mean BP changes Facial activity Body movements Quality of sleep Quality of contact with nurses Consolability Alertness Duration of crying	Intubation PIV insertion	Validated against NIPS and COMFORT Coefficient of variation: 33 ± 8%	Acute pain
Échelle Douleur Inconfort Nouveau-Né (EDIN) <sup>51</sup> (2001)	<i>N</i> = 76 Age: 25–36 wk GA	Quality of sleep Quality of contact with nurses Consolability Alertness Duration of crying	Acute and chronic ventilation; NEG, postoperative for PDA ligation	Patients served as controls Interrater reliability: coefficient range of 0.59–0.74 Internal consistency: Cronbach's $\alpha$ coefficients ranged from 0.86 to 0.94	Prolonged pain
Bernese Pain Scale for Neonates (BPSN) <sup>52</sup> (2004)	<i>N</i> = 12 Age: 27–41 wk GA	Quality of sleep Quality of contact with nurses Consolability Alertness Duration of crying	Heel lance	Validated against VAS and PIPP Concurrent and convergent validity: compared with VAS and PIPP was <i>r</i> = 0.86 and <i>r</i> = 0.91, respectively ( <i>P</i> < .0001) Interrater reliability: <i>r</i> = 0.86–0.97 Intrater reliability: <i>r</i> = 0.98–0.99	Acute pain
	288 pain assessments	Time to calm Skin color Eyebrow bulge with eye squeeze Posture Breathing pattern			

BP, blood pressure; CNS, central nervous system; desat, desaturation; DOL, days of life; FiO<sub>2</sub>, fraction of inspired oxygen; GA, gestational age; HR, heart rate; ICC, intraclass correlation coefficient; IV, intravenous (catheter); NEC, necrotizing enterocolitis; NG, nasogastric; PDA, patent ductus arteriosus; PIV, peripheral intravenous (line); RR, respiratory rate; sat, saturation; VAS, visual analog scale.

tool will be satisfactory for assessing neonatal pain for all situations and in infants of all gestational ages,<sup>39,57</sup> although initial validation studies have been published for the PIPP-Revised in infants with a gestational age of 25 to 41 weeks.<sup>40,41</sup> More research needs to be performed to assess the intensity of both acute and chronic pain at the bedside, to differentiate signs and symptoms of pain from those attributable to other causes, and to understand the significance of situations when there is no perceptible response to pain.<sup>40,41</sup> However, even with those limitations, one can use the available evidence to choose a pain assessment tool that is appropriate for the type of pain assessed (acute, prolonged, postoperative) and advocate for the competency of the neonatal care provider team with the specific use of that tool.<sup>58</sup> Table 1 lists commonly used pain assessment tools and the evidence used to test them.

## NONPHARMACOLOGIC TREATMENT STRATEGIES

Pediatricians and health care professionals who work with neonates have the difficult task of balancing the need for appropriate monitoring, testing, and treatment versus minimizing pain and stress to the patient. Nonpharmacologic strategies for pain management, such as swaddling combined with positioning, facilitated tucking (holding the infant in a flexed position with arms close to the trunk) with or without parental assistance, nonnutritive sucking, and massage, have all shown variable effectiveness in reducing pain and/or stress-related behaviors related to mild to moderately painful or stressful interventions.<sup>59–63</sup> A meta-analysis of 51 studies of nonpharmacologic interventions used during heel lance and intravenous catheter insertion found that sucking-related and swaddling/facilitated-tucking interventions were beneficial for

preterm neonates and that sucking-related and rocking/holding interventions were beneficial for term neonates, but that no benefit was evident among older infants.<sup>64</sup>

Skin-to-skin care (SSC), with or without sucrose or glucose administration, has been shown to decrease some measures of pain in preterm and term infants.<sup>65</sup> An analysis of 19 studies examining the effects of SSC on neonatal pain caused by single needle-related procedures found no statistical benefit for physiologic indicators of pain but did show benefit for composite pain score items.<sup>65</sup> However, some investigators have reported decreased cortisol concentrations and decreased autonomic indicators of pain in preterm infants during SSC, suggestive of a physiologic benefit.<sup>66,67</sup>

The effects of breastfeeding on pain response have also been investigated. A Cochrane systematic review published in 2012 found that breastfeeding during a heel lance or venipuncture was associated with significantly lower pain responses in term neonates (eg, smaller increases in heart rate and shorter crying time), compared with other nonpharmacologic interventions such as positioning, rocking, or maternal holding. Breastfeeding showed similar effectiveness to oral sucrose or glucose solutions.<sup>68</sup> This meta-analysis of 20 randomized controlled trials (RCTs)/quasi-RCTs also found that providing supplemental human milk via a pacifier or syringe seems to be as effective as providing sucrose or glucose for pain relief in term neonates.

Sensorial stimulation (SS), a method of gently stimulating the tactile, gustatory, auditory, and visual systems simultaneously, has shown effectiveness at decreasing pain during minor procedures such as heel lance.<sup>69</sup> SS is achieved by looking at and gently talking to the infant, while stroking or massaging the face

or back, and providing oral sucrose or glucose solution before a painful procedure. A systematic review of 16 studies found that SS was more effective than sucrose when all elements of SS were used,<sup>69</sup> and 1 study suggested that SS may play an important role in nonpharmacologic management of procedural pain for neonates.<sup>70</sup>

## PHARMACOLOGIC TREATMENT STRATEGIES

### Sucrose and Glucose

Oral sucrose is commonly used to provide analgesia to infants during mild to moderately painful procedures. It has been extensively studied for this purpose, yet many gaps in knowledge remain, including appropriate dosing, mechanism of action, soothing versus analgesic effects, and long-term consequences.<sup>71–73</sup> A meta-analysis of 57 studies including >4730 infants with gestational ages ranging from 25 to 44 weeks concluded that sucrose is safe and effective for reducing procedural pain from a single event.<sup>74</sup>

Maximum reductions in physiologic and behavioral pain indicators have been noted when sucrose was administered ~2 minutes before a painful stimulus, and the effects lasted ~4 minutes.<sup>74–76</sup> Procedures of longer duration, such as ophthalmologic examinations or circumcision, may require multiple doses of sucrose to provide continual analgesic effect.<sup>76</sup> In animal studies, the analgesic effects of sucrose appear to be a sweet-taste-mediated response of opiate, endorphin, and possibly dopamine or acetylcholine pathways; however, the mechanism of action is not well understood in human neonates.<sup>72,77–81</sup> An additive analgesic effect has been noted when sucrose is used in conjunction with other nonpharmacologic measures, such as nonnutritive sucking and swaddling, especially for procedures such as ophthalmologic examinations

and immunizations.<sup>74,78</sup> Although the evidence that oral sucrose alleviates procedurally related pain and stress, as judged by clinical pain scores, appears to be strong, a small RCT found no difference in either nociceptive brain activity on electroencephalography or spinal nociceptive reflex withdrawal on electromyography between sucrose or sterile water administered to term infants before a heel lance.<sup>73</sup> This masked study did find, however, that clinical pain scores were decreased in the infants receiving sucrose, and several methodologic concerns limit the conclusions that can be drawn from the trial.<sup>74</sup>

Sucrose use is common in most nurseries; however, doses vary widely.<sup>82</sup> Although an optimal dose has not been determined,<sup>74</sup> an oral dose of 0.1 to 1 mL of 24% sucrose (or 0.2–0.5 mL/kg) 2 minutes before a painful procedure has been recommended, taking into account gestational age, severity of illness, and procedure to be performed.<sup>71</sup> The role and safety of long-term sucrose use for persistent, ongoing pain have not been systematically studied. One study in 107 preterm infants of <31 weeks' gestation found worse neurodevelopmental scores at 32, 36, and 40 weeks' gestational age in infants who had received >10 doses of sucrose over a 24-hour period in the first week of life, raising concerns about frequent dosing in newly born preterm infants.<sup>83,84</sup> In addition, 1 infant in that study developed hyperglycemia coincident with frequent sucrose dosing, which may have been related to the sucrose or to subsequently diagnosed sepsis.<sup>83</sup> When sucrose is used as a pain management strategy, it should be prescribed and tracked as a medication. More research is needed to better understand the effects of sucrose use for analgesia.<sup>71,81,84</sup>

Glucose has also been found to be effective in decreasing response to brief painful procedures. A

meta-analysis of 38 RCTs that included 3785 preterm and term neonates found that the administration of 20% to 30% glucose solutions reduced pain scores and decreased crying during heel lance and venipuncture compared with water or no intervention. The authors concluded that glucose could be used as an alternative to sucrose solutions, although no recommendations about dose or timing of administration could be made.<sup>85</sup> As described for sucrose, however, glucose may not be effective for longer procedures. For example, an RCT found no effect of glucose on pain response during ophthalmologic examinations.<sup>86</sup>

### **Opioids, Benzodiazepines, and Other Drugs**

The most common pharmacologic agents used for pain relief in newborns are opioids, with fentanyl and morphine most often used, especially for persistent pain. Analgesics and sedatives are known to be potent modulators of several G-protein-linked receptor signaling pathways in the developing brain that are implicated in the critical regulation of neural tissue proliferation, survival, and differentiation. Studies of appropriate dosing and long-term effects of these analgesics given during the neonatal period are woefully lacking and/or conflicting.<sup>87,88</sup> However, in their absence, it remains critical to achieve adequate pain control in newborns, both as an ethical duty and because painful experiences in the NICU can have long-term adverse effects.<sup>7,10,19,20,89</sup>

Studies evaluating pharmacologic prevention and treatment of mild to moderate pain have generally been limited to a specific procedure such as intubation. The AAP recommends routine pain management during procedures such as circumcision,<sup>90</sup> chest drain insertion and removal,<sup>2</sup> and nonemergency intubations.<sup>91</sup>

However, effective management strategies for pain and sedation during mechanical ventilation remain elusive. A recent systematic review reported limited favorable effect with selective rather than routine use of opioids for analgesia in mechanically ventilated infants.<sup>92</sup> Concerns have been raised for adverse short- and long-term neurodevelopmental outcomes related to the use of morphine infusions in preterm neonates.<sup>92,93</sup> However, a follow-up study in ninety 8- to 9-year-olds who had previously participated in 1 RCT comparing continuous morphine infusion with placebo found that low-dose morphine infusion did not affect cognition or behavior and may have had a positive effect on everyday executive functions for these children.<sup>87</sup>

A 2008 Cochrane systematic review found insufficient evidence to recommend the routine use of opioids in mechanically ventilated infants.<sup>94</sup> Although there appeared to be a reduction in pain, there were no long-term benefits favoring the treatment groups; and concerns for adverse effects, such as respiratory depression, increase in the duration of mechanical ventilation, and development of dependence and tolerance, were raised. Other short-term physiologic adverse effects of concern included hypotension, constipation, and urinary retention for morphine and bradycardia and chest wall rigidity for fentanyl.<sup>94</sup> Remifentanyl, a shorter-acting fentanyl derivative, may be an alternative for short-term procedures and surgeries because it is not cleared by liver metabolism, but there are no studies examining its long-term effects.<sup>95,96</sup>

Benzodiazepines, most commonly midazolam, are frequently used in the NICU for sedation. However, because there is evidence of only minor additional analgesic effect, they may not provide much benefit. These agents can potentiate the respiratory

depression and hypotension that can occur with opioids, and infants receiving them should be carefully monitored.<sup>97</sup> Midazolam was associated with adverse short-term effects in the NOPAIN (Neonatal Outcome and Prolonged Analgesia in Neonates) trial.<sup>98</sup> A systematic review in 2012 found insufficient evidence to recommend midazolam infusions for sedation in the NICU and raised safety concerns, particularly regarding neurotoxicity.<sup>97</sup>

Alternative medications, such as methadone,<sup>99</sup> ketamine, propofol, and dexmedetomidine, have been proposed for pain management in neonates; however, few, if any, studies of these agents have been performed in this population, and caution should be exercised when considering them for use because of concerns about unanticipated adverse effects and potential neurotoxic effects.<sup>100</sup> Although the potential benefits of using methadone for the treatment of neonatal pain include satisfactory analgesic effects and enteral bioavailability as well as prolonged duration of action related to its long half-life and lower expense compared with other opiates, safe and effective dosing regimens have yet to be developed.<sup>101</sup> Ketamine is a dissociative anesthetic that, in lower doses, provides good analgesia, amnesia, and sedation.<sup>102</sup> Although ketamine has been well studied in older populations, further research is needed to establish safety profiles for use in neonates because of concerns regarding possible neurotoxicity.<sup>103</sup> Propofol has been used for short procedural sedation in children because of its rapid onset and clearance. The clearance of propofol in the neonatal population is inversely related to postmenstrual age, with significant variability in its pharmacokinetics in preterm and term neonates.<sup>104</sup> It has also been associated with bradycardia, desaturations, and

prolonged hypotension in newborn infants.<sup>105</sup> Limited experience with dexmedetomidine in preterm and term infants suggests that it may provide effective sedation and analgesia. Preliminary pharmacokinetic data showed decreased clearance in preterm infants compared with term infants and a favorable safety profile over a 24-hour period.<sup>106</sup>

The use of oral or intravenous acetaminophen has been limited to postoperative pain control. Although intravenous acetaminophen has not been approved by the US Food and Drug Administration, preliminary data on its safety and efficacy are promising in neonates and infants and it may decrease the total amount of morphine needed to treat postoperative pain.<sup>107-109</sup> Nonsteroidal antiinflammatory medication use has been restricted to pharmacologic closure of patent ductus arteriosus because of concerns regarding renal insufficiency, platelet dysfunction, and the development of pulmonary hypertension.<sup>110</sup> An animal study suggests that cyclooxygenase-1 inhibitors are less effective in immature compared with mature animals, probably because of decreased cyclooxygenase-1 receptor expression in the spinal cord.<sup>110</sup> This decrease in receptor expression may explain the lack of efficacy of nonsteroidal antiinflammatory drugs in human infants.<sup>111</sup>

### Topical Anesthetic Agents

Topical anesthesia may provide pain relief during some procedures. The most commonly studied and used topical agents in the neonatal population are tetracaine gel and Eutectic Mixture of Local Anesthetics (EMLA), a mixture of 2.5% lidocaine and 2.5% prilocaine. These agents have been found to decrease measures of pain during venipuncture, percutaneous central venous catheter insertion, and

peripheral arterial puncture.<sup>112-114</sup> EMLA did not decrease pain-related measures during heel lance<sup>113</sup> but may decrease pain measures during lumbar puncture,<sup>115</sup> particularly if the patient is concurrently provided with oral sucrose or glucose solution.<sup>116</sup> Concerns related to the use of topical anesthetics include methemoglobinemia, prolonged application times to allow absorption for optimal effectiveness, local skin irritation, and toxicity, especially in preterm infants.<sup>117,118</sup>

## CONCLUSIONS AND RECOMMENDATIONS

In summary, there are significant research gaps regarding the assessment, management, and outcomes of neonatal pain; and there is a continuing need for studies evaluating the effects of neonatal pain and pain-prevention strategies on long-term neurodevelopmental, behavioral, and cognitive outcomes. The use of pharmacologic treatments for pain prevention and management in neonates continues to be hampered by the paucity of data on the short- and long-term safety and efficacy of these agents. At the same time, repetitive pain in the NICU has been associated with adverse neurodevelopmental, behavioral, and cognitive outcomes, calling for more research to address gaps in knowledge.<sup>5,8,22,89,119-122</sup> Despite incomplete data, the pediatrician and other health care professionals who care for neonates face the need to weigh both of these concerns in assessing pain and the need for pain prevention and management on a continuing basis throughout the infant's hospitalization.

### Recommendations

1. Preventing or minimizing pain in neonates should be the goal of pediatricians and other health care professionals who care for neonates. To facilitate this goal, each institution should



have written guidelines, based on existing and emerging evidence, for a stepwise pain-prevention and treatment plan, which includes judicious use of procedures, routine assessment of pain, use of both pharmacologic and nonpharmacologic therapies for the prevention of pain associated with routine minor procedures, and effective medications to minimize pain associated with surgery and other major procedures.

2. Despite the significant challenges of assessing pain in this population, currently available, validated neonatal pain assessment tools should be consistently used before, during, and after painful procedures to monitor the effectiveness of pain relief interventions. In addition, the need for pain prevention and management should be assessed on a continuing basis throughout the infant's hospitalization.
3. Nonpharmacologic strategies, such as facilitated tucking, nonnutritive sucking, provision of breastfeeding or providing expressed human milk, or SS have been shown to be useful in decreasing pain scores during short-term mild to moderately painful procedures and should be consistently used.
4. Oral sucrose and/or glucose solutions can be effective in neonates undergoing mild to moderately painful procedures, either alone or in combination with other pain relief strategies. When sucrose or glucose is used as a pain management strategy, it should be prescribed and tracked as a medication; evidence-based protocols should be developed and implemented in nurseries, and more research should be conducted to better understand the effects of sucrose use for analgesia.

5. The pediatrician and other health care professionals who care for neonates must weigh potential and actual benefits and burdens when using pharmacologic treatment methods based on available evidence. Some medications can potentiate the respiratory depression and hypotension that can occur with opioids, and infants receiving them should be carefully monitored. Caution should be exercised when considering newer medications for which data in neonates are sparse or nonexistent.
6. Pediatricians, other neonatal health care providers, and family members should receive continuing education regarding the recognition, assessment, and management of pain in neonates, including new evidence as it becomes available.
7. To address the gaps in knowledge, more research should be conducted on pain assessment tools and pharmacologic and nonpharmacologic strategies to prevent or ameliorate pain. Studies on pharmacokinetics and pharmacodynamics of newer medications are needed to prevent therapeutic misadventures in the most vulnerable patients in pediatric practice.

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#### ABBREVIATIONS

AAP: American Academy of Pediatrics  
PIPP: Premature Infant Pain Profile  
RCT: randomized controlled trial  
SS: sensorial stimulation  
SSC: skin-to-skin care

#### REFERENCES

1. American Academy of Pediatrics Committee on Fetus and Newborn, Committee on Drugs, Section on Anesthesiology, Section on Surgery; Canadian Paediatric Society Fetus and Newborn Committee. Prevention and management of pain and stress in the neonate. *Pediatrics*. 2000;105(2):454–461
2. Batton DG, Barrington KJ, Wallman C; American Academy of Pediatrics

- Committee on Fetus and Newborn; American Academy of Pediatrics Section on Surgery; Canadian Paediatric Society Fetus and Newborn Committee. Prevention and management of pain in the neonate: an update. *Pediatrics*. 2006;118(5):2231–2241
3. Carbajal R, Rousset A, Danan C, et al. Epidemiology and treatment of painful procedures in neonates in intensive care units. *JAMA*. 2008;300(1):60–70
  4. Simons SH, van Dijk M, Anand KS, Roofthoof D, van Lingen RA, Tibboel D. Do we still hurt newborn babies? A prospective study of procedural pain and analgesia in neonates. *Arch Pediatr Adolesc Med*. 2003;157(11):1058–1064
  5. Anand KJ, Aranda JV, Berde CB, et al. Summary proceedings from the neonatal pain-control group. *Pediatrics*. 2006;117(3 Suppl 1):S9–S22
  6. Anand KJ. Clinical importance of pain and stress in preterm neonates. *Biol Neonate*. 1998;73(1):1–9
  7. Vinall J, Grunau RE. Impact of repeated procedural pain-related stress in infants born very preterm. *Pediatr Res*. 2014;75(5):584–587
  8. Doesburg SM, Chau CM, Cheung TP, et al. Neonatal pain-related stress, functional cortical activity and visual-perceptual abilities in school-age children born at extremely low gestational age. *Pain*. 2013;154(10):1946–1952
  9. Hermann C, Hohmeister J, Demirakça S, Zohsel K, Flor H. Long-term alteration of pain sensitivity in school-aged children with early pain experiences. *Pain*. 2006;125(3):278–285
  10. Grunau RE, Whitfield MF, Petrie-Thomas J, et al. Neonatal pain, parenting stress and interaction, in relation to cognitive and motor development at 8 and 18 months in preterm infants. *Pain*. 2009;143(1–2):138–146
  11. Walker SM, Franck LS, Fitzgerald M, Myles J, Stocks J, Marlow N. Long-term impact of neonatal intensive care and surgery on somatosensory perception in children born extremely preterm. *Pain*. 2009;141(1–2):79–87
  12. Beggs S, Torsney C, Drew LJ, Fitzgerald M. The postnatal reorganization of primary afferent input and dorsal horn cell receptive fields in the rat spinal cord is an activity-dependent process. *Eur J Neurosci*. 2002;16(7):1249–1258
  13. Jennings E, Fitzgerald M. Postnatal changes in responses of rat dorsal horn cells to afferent stimulation: a fibre-induced sensitization. *J Physiol*. 1998;509(pt 3):859–868
  14. Schmelzle-Lubiecki BM, Campbell KA, Howard RH, Franck L, Fitzgerald M. Long-term consequences of early infant injury and trauma upon somatosensory processing. *Eur J Pain*. 2007;11(7):799–809
  15. Ranger M, Chau CM, Garg A, et al. Neonatal pain-related stress predicts cortical thickness at age 7 years in children born very preterm. *PLoS One*. 2013;8(10):e76702
  16. Slater R, Cantarella A, Gallella S, et al. Cortical pain responses in human infants. *J Neurosci*. 2006;26(14):3662–3666
  17. Ingram RA, Fitzgerald M, Baccei ML. Developmental changes in the fidelity and short-term plasticity of GABAergic synapses in the neonatal rat dorsal horn. *J Neurophysiol*. 2008;99(6):3144–3150
  18. Walker SM, Meredith-Middleton J, Lickiss T, Moss A, Fitzgerald M. Primary and secondary hyperalgesia can be differentiated by postnatal age and ERK activation in the spinal dorsal horn of the rat pup. *Pain*. 2007;128(1–2):157–168
  19. Holsti L, Grunau RE, Oberlander TF, Whitfield MF. Prior pain induces heightened motor responses during clustered care in preterm infants in the NICU. *Early Hum Dev*. 2005;81(3):293–302
  20. Grunau RE, Holsti L, Haley DW, et al. Neonatal procedural pain exposure predicts lower cortisol and behavioral reactivity in preterm infants in the NICU. *Pain*. 2005;113(3):293–300
  21. Cignacco E, Hamers J, van Lingen RA, et al. Neonatal procedural pain exposure and pain management in ventilated preterm infants during the first 14 days of life. *Swiss Med Wkly*. 2009;139(15–16):226–232
  22. Bouza H. The impact of pain in the immature brain. *J Matern Fetal Neonatal Med*. 2009;22(9):722–732
  23. Bellieni CV, Iantorno L, Perrone S, et al. Even routine painful procedures can be harmful for the newborn. *Pain*. 2009;147(1–3):128–131
  24. Slater L, Asmerom Y, Boskovic DS, et al. Procedural pain and oxidative stress in premature neonates. *J Pain*. 2012;13(6):590–597
  25. Fitzgerald M. The development of nociceptive circuits. *Nat Rev Neurosci*. 2005;6(7):507–520
  26. Hohmeister J, Demirakça S, Zohsel K, Flor H, Hermann C. Responses to pain in school-aged children with experience in a neonatal intensive care unit: cognitive aspects and maternal influences. *Eur J Pain*. 2009;13(1):94–101
  27. Grunau RE, Whitfield MF, Fay TB. Psychosocial and academic characteristics of extremely low birth weight (< or =800 g) adolescents who are free of major impairment compared with term-born control subjects. *Pediatrics*. 2004;114(6). Available at: [www.pediatrics.org/cgi/content/full/114/6/e725](http://www.pediatrics.org/cgi/content/full/114/6/e725)
  28. Anand KJ; 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
  29. Hummel P, van Dijk M. Pain assessment: current status and challenges. *Semin Fetal Neonatal Med*. 2006;11(4):237–245
  30. Grunau RE, Oberlander T, Holsti L, Whitfield MF. Bedside application of the Neonatal Facial Coding System in pain assessment of premature neonates. *Pain*. 1998;76(3):277–286
  31. Peters JW, Koot HM, Grunau RE, et al. Neonatal Facial Coding System for assessing postoperative pain in infants: item reduction is valid and feasible. *Clin J Pain*. 2003;19(6):353–363
  32. Stevens B, Johnston C, Petryshen P, Taddio A. Premature Infant Pain Profile: development and initial validation. *Clin J Pain*. 1996;12(1):13–22

33. Ballantyne M, Stevens B, McAllister M, Dionne K, Jack A. Validation of the premature infant pain profile in the clinical setting. *Clin J Pain*. 1999;15(4):297–303
34. Jonsdottir RB, Kristjansdottir G. The sensitivity of the Premature Infant Pain Profile—PIPP to measure pain in hospitalized neonates. *J Eval Clin Pract*. 2005;11(6):598–605
35. Hummel P, Puchalski M, Creech SD, Weiss MG. Clinical reliability and validity of the N-PASS: neonatal pain, agitation and sedation scale with prolonged pain. *J Perinatol*. 2008;28(1):55–60
36. Hummel P, Lawlor-Klean P, Weiss MG. Validity and reliability of the N-PASS assessment tool with acute pain. *J Perinatol*. 2010;30(7):474–478
37. Holsti L, Grunau RE. Initial validation of the Behavioral Indicators of Infant Pain (BIIP). *Pain*. 2007;132(3):264–272
38. Carbajal R, Paupe A, Hoenn E, Lenclen R, Olivier-Martin M. [APN: evaluation behavioral scale of acute pain in newborn infants.] [Article in French]. *Arch Pediatr*. 1997;4(7):623–628
39. Cong X, McGrath JM, Cusson RM, Zhang D. Pain assessment and measurement in neonates: an updated review. *Adv Neonatal Care*. 2013;13(6):379–395
40. Stevens BJ, Gibbins S, Yamada J, et al. The premature infant pain profile-revised (PIPP-R): initial validation and feasibility. *Clin J Pain*. 2014;30(3):238–243
41. Gibbins S, Stevens BJ, Yamada J, et al. Validation of the Premature Infant Pain Profile-Revised (PIPP-R). *Early Hum Dev*. 2014;90(4):189–193
42. Milesi C, Cambonie G, Jacquot A, et al. Validation of a neonatal pain scale adapted to the new practices in caring for preterm newborns. *Arch Dis Child Fetal Neonatal Ed*. 2010;95(4):F263–F266
43. Lawrence J, Alcock D, McGrath P, Kay J, MacMurray SB, Dulberg C. The development of a tool to assess neonatal pain. *Neonatal Netw*. 1993;12(6):59–66
44. Krechel SW, Bildner J. CRIES: a new neonatal postoperative pain measurement score. Initial testing of validity and reliability. *Paediatr Anaesth*. 1995;5(1):53–61
45. van Dijk M, Roofthoof DW, Anand KJ, et al. Taking up the challenge of measuring prolonged pain in (premature) neonates: the COMFORTneo scale seems promising. *Clin J Pain*. 2009;25(7):607–616
46. Hand I, Noble L, Geiss D, Wozniak L, Hall C. COVERS Neonatal Pain Scale: development and validation. *Int J Pediatr*. 2010. Available at: www.hindawi.com/journals/ijpedi/2010/496719/. Accessed December 17, 2014
47. Hudson-Barr D, Capper-Michel B, Lambert S, Palermo TM, Morbeto K, Lombardo S. Validation of the Pain Assessment in Neonates (PAIN) scale with the Neonatal Infant Pain Scale (NIPS). *Neonatal Netw*. 2002;21(6):15–21
48. Hodgkinson K, Bear M, Thorn J, Van Blaricum S. Measuring pain in neonates: evaluating an instrument and developing a common language. *Aust J Adv Nurs*. 1994;12(1):17–22
49. Spence K, Gillies D, Harrison D, Johnston L, Nagy S. A reliable pain assessment tool for clinical assessment in the neonatal intensive care unit. *J Obstet Gynecol Neonatal Nurs*. 2005;34(1):80–86
50. Blauer T, Gerstmann D. A simultaneous comparison of three neonatal pain scales during common NICU procedures. *Clin J Pain*. 1998;14(1):39–47
51. Debillon T, Zupan V, Ravault N, Magny JF, Dehan M. Development and initial validation of the EDIN scale, a new tool for assessing prolonged pain in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2001;85(1):F36–F41
52. Cignacco E, Mueller R, Hamers JP, Gessler P. Pain assessment in the neonate using the Bernese Pain Scale for Neonates. *Early Hum Dev*. 2004;78(2):125–131
53. Slater R, Cantarella A, Franck L, Meek J, Fitzgerald M. How well do clinical pain assessment tools reflect pain in infants? *PLoS Med*. 2008;5(6):e129
54. Smith GC, Gutovich J, Smyser C, et al. Neonatal intensive care unit stress is associated with brain development in preterm infants. *Ann Neurol*. 2011;70(4):541–549
55. Hünseler C, Merkt V, Gerloff M, Eifinger F, Kribs A, Roth B. Assessing pain in ventilated newborns and infants: validation of the Hartwig score. *Eur J Pediatr*. 2011;170(7):837–843
56. Arias MC, Guinsburg R. Differences between uni-and multidimensional scales for assessing pain in term newborn infants at the bedside. *Clinics (Sao Paulo)*. 2012;67(10):1165–1170
57. Ahn Y, Jun Y. Measurement of pain-like response to various NICU stimulants for high-risk infants. *Early Hum Dev*. 2007;83(4):255–262
58. Walden M, Gibbins S. *Pain Assessment and Management: Guidelines for Practice*. 2nd ed. Glenview, IL: National Association of Neonatal Nurses; 2010
59. Morrow C, Hidingen A, Wilkinson-Faulk D. Reducing neonatal pain during routine heel lance procedures. *MCN Am J Matern Child Nurs*. 2010;35(6):346–354; quiz: 354–356
60. Axelin A, Salanterä S, Kirjavainen J, Lehtonen L. Oral glucose and parental holding preferable to opioid in pain management in preterm infants. *Clin J Pain*. 2009;25(2):138–145
61. Obeidat H, Kahalaf I, Callister LC, Froelicher ES. Use of facilitated tucking for nonpharmacological pain management in preterm infants: a systematic review. *J Perinat Neonatal Nurs*. 2009;23(4):372–377
62. Liaw JJ, Yang L, Katherine Wang KW, Chen CM, Chang YC, Yin T. Non-nutritive sucking and facilitated tucking relieve preterm infant pain during heel-stick procedures: a prospective, randomised controlled crossover trial. *Int J Nurs Stud*. 2012;49(3):300–309
63. Abdallah B, Badr LK, Hawwari M. The efficacy of massage on short and long term outcomes in preterm infants. *Infant Behav Dev*. 2013;36(4):662–669
64. Pillai Riddell RR, Racine NM, Turcotte K, et al. Non-pharmacological management of infant and young child procedural pain. *Cochrane Database Syst Rev*. 2011;2011(10):CD006275
65. Johnston C, Campbell-Yeo M, Fernandes A, Inglis D, Streiner D, Zee R. Skin-to-skin care for procedural pain

- in neonates. *Cochrane Database Syst Rev*. 2014;1(1):CD008435
66. Cong X, Cusson RM, Walsh S, Hussain N, Ludington-Hoe SM, Zhang D. Effects of skin-to-skin contact on autonomic pain responses in preterm infants. *J Pain*. 2012;13(7):636–645
  67. Cong X, Ludington-Hoe SM, Walsh S. Randomized crossover trial of kangaroo care to reduce biobehavioral pain responses in preterm infants: a pilot study. *Biol Res Nurs*. 2011;13(2):204–216
  68. Shah PS, Herbozo C, Aliwalas LL, Shah VS. Breastfeeding or breast milk for procedural pain in neonates. *Cochrane Database Syst Rev*. 2012;12(12):CD004950
  69. Bellieni CV, Tei M, Coccina F, Buonocore G. Sensorial saturation for infants' pain. *J Matern Fetal Neonatal Med*. 2012;25(suppl 1):79–81
  70. Gitto E, Pellegrino S, Manfrida M, et al. Stress response and procedural pain in the preterm newborn: the role of pharmacological and non-pharmacological treatments. *Eur J Pediatr*. 2012;171(6):927–933
  71. Harrison D, Beggs S, Stevens B. Sucrose for procedural pain management in infants. *Pediatrics*. 2012;130(5):918–925
  72. Slater R, Cornelissen L, Fabrizi L, et al. Oral sucrose as an analgesic drug for procedural pain in newborn infants: a randomised controlled trial. *Lancet*. 2010;376(9748):1225–1232
  73. Wilkinson DJ, Savulescu J, Slater R. Sugaring the pill: ethics and uncertainties in the use of sucrose for newborn infants. *Arch Pediatr Adolesc Med*. 2012;166(7):629–633
  74. Stevens B, Yamada J, Lee GY, Ohlsson A. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev*. 2013;1(1):CD001069
  75. Lefrak L, Burch K, Caravantes R, et al. Sucrose analgesia: identifying potentially better practices. *Pediatrics*. 2006;118(2 suppl 2):S197–S202
  76. Johnston CC, Stremler R, Horton L, Friedman A. Effect of repeated doses of sucrose during heel stick procedure in preterm neonates. *Biol Neonate*. 1999;75(3):160–166
  77. Fernandez M, Blass EM, Hernandez-Reif M, Field T, Diego M, Sanders C. Sucrose attenuates a negative electroencephalographic response to an aversive stimulus for newborns. *J Dev Behav Pediatr*. 2003;24(4):261–266
  78. Blass EM, Watt LB. Suckling- and sucrose-induced analgesia in human newborns. *Pain*. 1999;83(3):611–623
  79. Shide DJ, Blass EM. Opioidlike effects of intraoral infusions of corn oil and polydose on stress reactions in 10-day-old rats. *Behav Neurosci*. 1989;103(6):1168–1175
  80. Anseloni VC, Ren K, Dubner R, Ennis M. A brainstem substrate for analgesia elicited by intraoral sucrose. *Neuroscience*. 2005;133(1):231–243
  81. Holsti L, Grunau RE. Considerations for using sucrose to reduce procedural pain in preterm infants. *Pediatrics*. 2010;125(5):1042–1047
  82. Taddio A, Yiu A, Smith RW, Katz J, McNair C, Shah V. Variability in clinical practice guidelines for sweetening agents in newborn infants undergoing painful procedures. *Clin J Pain*. 2009;25(2):153–155
  83. Johnston CC, Filion F, Snider L, et al. Routine sucrose analgesia during the first week of life in neonates younger than 31 weeks' postconceptional age. *Pediatrics*. 2002;110(3):523–528
  84. Johnston CC, Filion F, Snider L, et al. How much sucrose is too much sucrose [letter]? *Pediatrics*. 2007;119(1):226
  85. Bueno M, Yamada J, Harrison D, et al. A systematic review and meta-analyses of nonsucrose sweet solutions for pain relief in neonates. *Pain Res Manag*. 2013;18(3):153–161
  86. Costa MC, Eckert GU, Fortes BG, Fortes Filho JB, Silveira RC, Procianny RS. Oral glucose for pain relief during examination for retinopathy of prematurity: a masked randomized clinical trial. *Clinics (Sao Paulo)*. 2013;68(2):199–204
  87. de Graaf J, van Lingen RA, Valkenburg AJ, et al. Does neonatal morphine use affect neuropsychological outcomes at 8 to 9 years of age? *Pain*. 2013;154(3):449–458
  88. Rozé JC, Denizot S, Carbajal R, et al. Prolonged sedation and/or analgesia and 5-year neurodevelopment outcome in very preterm infants: results from the EPIPAGE cohort. *Arch Pediatr Adolesc Med*. 2008;162(8):728–733
  89. Whitfield MF, Grunau RE. Behavior, pain perception, and the extremely low-birth weight survivor. *Clin Perinatol*. 2000;27(2):363–379
  90. American Academy of Pediatrics, Task Force on Circumcision. Circumcision policy statement. *Pediatrics*. 1999;103(3):686–693
  91. Kumar P, Denson SE, Mancuso TJ; Committee on Fetus and Newborn, Section on Anesthesiology and Pain Medicine. Premedication for nonemergency endotracheal intubation in the neonate. *Pediatrics*. 2010;125(3):608–615
  92. Bellù R, de Waal K, Zanini R. Opioids for neonates receiving mechanical ventilation: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed*. 2010;95(4):F241–F251
  93. Anand KJ, Hall RW, Desai N, et al; NEOPAIN Trial Investigators Group. Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial. *Lancet*. 2004;363(9422):1673–1682
  94. Bellù R, de Waal KA, Zanini R. Opioids for neonates receiving mechanical ventilation. *Cochrane Database Syst Rev*. 2008;1:CD004212
  95. Choong K, AlFaleh K, Doucette J, et al. Remifentanyl for endotracheal intubation in neonates: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed*. 2010;95(2):F80–F84
  96. Lago P, Tiozzo C, Boccuzzo G, Allegro A, Zaccello F. Remifentanyl for percutaneous intravenous central catheter placement in preterm infant: a randomized controlled trial. *Paediatr Anaesth*. 2008;18(8):736–744
  97. Ng E, Taddio A, Ohlsson A. Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. *Cochrane Database Syst Rev*. 2012;6(6):CD002052
  98. Anand KJ, Barton BA, McIntosh N, et al. Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. *Neonatal Outcome and Prolonged*

- Analgesia in Neonates. *Arch Pediatr Adolesc Med.* 1999;153(4):331–338
99. Anand KJ. Pharmacological approaches to the management of pain in the neonatal intensive care unit. *J Perinatol.* 2007;27(suppl 1):S4–S11
  100. Durrmeyer X, Vutskits L, Anand KJ, Rimensberger PC. Use of analgesic and sedative drugs in the NICU: integrating clinical trials and laboratory data. *Pediatr Res.* 2010;67(2):117–127
  101. Chana SK, Anand KJ. Can we use methadone for analgesia in neonates? *Arch Dis Child Fetal Neonatal Ed.* 2001;85(2):F79–F81
  102. Nemergut ME, Yaster M, Colby CE. Sedation and analgesia to facilitate mechanical ventilation. *Clin Perinatol.* 2013;40(3):539–558
  103. Cravero JP, Havidich JE. Pediatric sedation—evolution and revolution. *Paediatr Anaesth.* 2011;21(7):800–809
  104. Allegaert K, Peeters MY, Verbesselt R, et al. Inter-individual variability in propofol pharmacokinetics in preterm and term neonates. *Br J Anaesth.* 2007;99(6):864–870
  105. Vanderhaegen J, Naulaers G, Van Huffel S, Vanhole C, Allegaert K. Cerebral and systemic hemodynamic effects of intravenous bolus administration of propofol in neonates. *Neonatology.* 2010;98(1):57–63
  106. Chrysostomou C, Schulman SR, Herrera Castellanos M, et al. A phase II/III, multicenter, safety, efficacy, and pharmacokinetic study of dexmedetomidine in preterm and term neonates. *J Pediatr.* 2014;164(2):276–282
  107. Allegaert K, van den Anker J. Pharmacokinetics and pharmacodynamics of intravenous acetaminophen in neonates. *Expert Rev Clin Pharmacol.* 2011;4(6):713–718
  108. Ceelie I, de Wildt SN, van Dijk M, et al. Effect of intravenous paracetamol on postoperative morphine requirements in neonates and infants undergoing major noncardiac surgery: a randomized controlled trial. *JAMA.* 2013;309(2):149–154
  109. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for prevention or treatment of pain in newborns. *Cochrane Database Syst Rev.* 2015;6(6):CD011219
  110. Ohlsson A, Walia R, Shah S. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. *Cochrane Database Syst Rev.* 2008;1:CD003481
  111. Ririe DG, Prout HD, Barclay D, Tong C, Lin M, Eisenach JC. Developmental differences in spinal cyclooxygenase 1 expression after surgical incision. *Anesthesiology.* 2006;104(3):426–431
  112. Taddio A, Ohlsson A, Einarson TR, Stevens B, Koren G. A systematic review of lidocaine-prilocaine cream (EMLA) in the treatment of acute pain in neonates. *Pediatrics.* 1998;101(2):e1
  113. Kapellou O. Blood sampling in infants (reducing pain and morbidity). 2011;Apr 5: 2011. pii: 0313
  114. Hall RW, Anand KJ. Pain management in newborns. *Clin Perinatol.* 2014;41(4):895–924
  115. Kaur G, Gupta P, Kumar A. A randomized trial of eutectic mixture of local anesthetics during lumbar puncture in newborns. *Arch Pediatr Adolesc Med.* 2003;157(11):1065–1070
  116. Biran V, Gourrier E, Cimerman P, Walter-Nicolet E, Mitanchez D, Carbajal R. Analgesic effects of EMLA cream and oral sucrose during venipuncture in preterm infants. *Pediatrics.* 2011;128(1). Available at: [www.pediatrics.org/cgi/content/full/128/1/e63](http://www.pediatrics.org/cgi/content/full/128/1/e63)
  117. Foster JP, Taylor C, Bredemeyer SL. Topical anaesthesia for needle-related pain in newborn infants. *Cochrane Database Syst Rev.* 2013; (1):CD010331
  118. Maulidi H, McNair C, Seller N, Kirsh J, Bradley TJ, Greenway SC, Tomlinson C. Arrhythmia associated with tetracaine in an extremely low birth weight premature infant. *Pediatrics.* 2012;130(6). Available at: [www.pediatrics.org/cgi/content/full/130/6/e1704](http://www.pediatrics.org/cgi/content/full/130/6/e1704)
  119. Harrison D, Yamada J, Stevens B. Strategies for the prevention and management of neonatal and infant pain. *Curr Pain Headache Rep.* 2010;14(2):113–123
  120. Grunau R. Early pain in preterm infants: a model of long-term effects. *Clin Perinatol.* 2002;29(3):373–394, vii–viii
  121. Taddio A, Shah V, Gilbert-MacLeod C, Katz J. Conditioning and hyperalgesia in newborns exposed to repeated heel lances. *JAMA.* 2002;288(7):857–861
  122. Anand KJ, Johnston CC, Oberlander TF, Taddio A, Lehr VT, Walco GA. Analgesia and local anesthesia during invasive procedures in the neonate. *Clin Ther.* 2005;27(6):844–876

**Prevention and Management of Procedural Pain in the Neonate: An Update**  
COMMITTEE ON FETUS AND NEWBORN and SECTION ON  
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