Neonatal Abstinence Syndrome: Reconsidering the Standard Approach

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DISCLOSURE

The content of this presentation does not relate to any product of a commercial entity; therefore, I have no relationships to report.

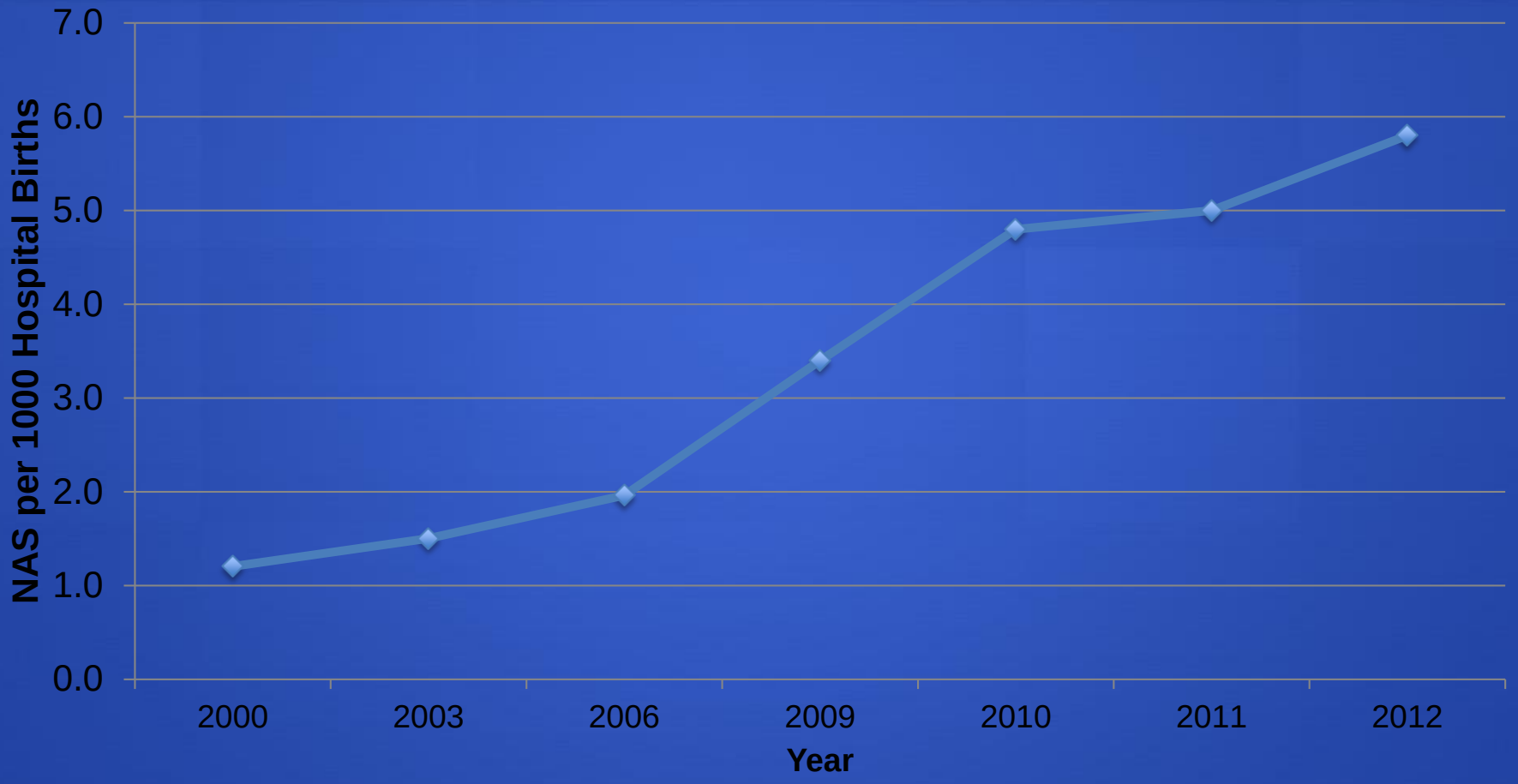
Opioids in the US

- Prescriptions grew 4-fold over last decade
- More deaths than car accidents
  - 91 people die each day from opioids
- In 2012, enough opioids were prescribed to give every adult in the US one prescription

Patrick, et al. Journal of Perinatology. 2015; 35:650-655

Source: http://familytalk.ca/heroin/

Incidence of NAS in the US, 2000-2012



Patrick SW, et. al. Neonatal Abstinence Syndrome and Associated Healthcare Expenditures – United States, 2000-2009. *JAMA*. 2012 May 9;307(18):1934-40.

Patrick SW, Davis MM, Lehman CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. J Perinatol. Apr 30 2015.

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Increasing Incidence of the Neonatal Abstinence Syndrome in U.S. Neonatal ICUs

Veeral N. Tolia, M.D., Stephen W. Patrick, M.D., M.P.H., Monica M. Bennett, Ph.D., Karna Murthy, M.D., John Sousa, B.S., P. Brian Smith, M.D., M.P.H., M.H.S., Reese H. Clark, M.D., and Alan R. Spitzer, M.D.

ABSTRACT

BACKGROUND

The incidence of the neonatal abstinence syndrome, a drug-withdrawal syndrome that most commonly occurs after in utero exposure to opioids, is known to have


Source: Grossman Family Album

SYSTEMS	SIGNS AND SYMPTOMS	SCORE	AM 2	4	6	8	10	12	PM 2	4	6	8	10	12	DAILY WT.
CENTRAL NERVOUS SYSTEM DISTURBANCES	High Pitched Cry Continuous High Pitched Cry	2 3													
	Sleeps < 1 Hour After Feeding Sleeps < 2 Hours After Feeding	3 2													
	Hyperactive Moro Reflex Markedly Hyperactive Moro Reflex	2 3													
	Mild Tremors Disturbed Moderate Severe Tremors Disturbed	2 3													
	Mild Tremors Undisturbed Moderate Severe Tremors Undisturbed	1 2													
	Increased Muscle Tone	2													
	Excoriation (specify area): _____	1													
	Myoclonic Jerks	3													
	Generalized Convulsions	3													
METABOLIC VASOMOTOR/ RESPIRATORY DISTURBANCES	Sweating	1													
	Fever < 101°F (39.3°C) Fever > 101°F (39.3°C)	1 2													
	Frequent Yawning (> 3–4 times/interval)	1													
	Mottling	1													
	Nasal Stuffiness	1													
	Sneezing (> 3–4 times/interval)	1													
	Nasal Flaring	2													
	Respiratory Rate > 60/min Respiration Rate > 60/min with Retractions	1 2													
GASTROINTESTINAL DISTURBANCES	Excessive Sucking	1													
	Poor Feeding	2													
	Regurgitation Projectile Vomiting	2 3													
	Loose Stools Watery Stools	2 3													
SUMMARY	**TOTAL SCORE**														
	SCORER'S INITIALS														
	STATUS OF THERAPY														

Adapted from Finnegan L. Neonatal abstinence syndrome: assessment and pharmacotherapy. Neonatal Therapy: An update, F. F. Rubaltelli and B. Granti, editors. Elsevier Science Publishers B. V. (Biomedical Division). 1986: 122-146

Source: http://wings.buffalo.edu/aru/preprohibition.htm

Langenfeld, et al. Drug and Alcohol Dependence 2005;77:31–6.

Source: http://olivier-dogot.blogspot.com

Jackson L, et al. Archives of Disease in Childhood 2004;89: F300–4.

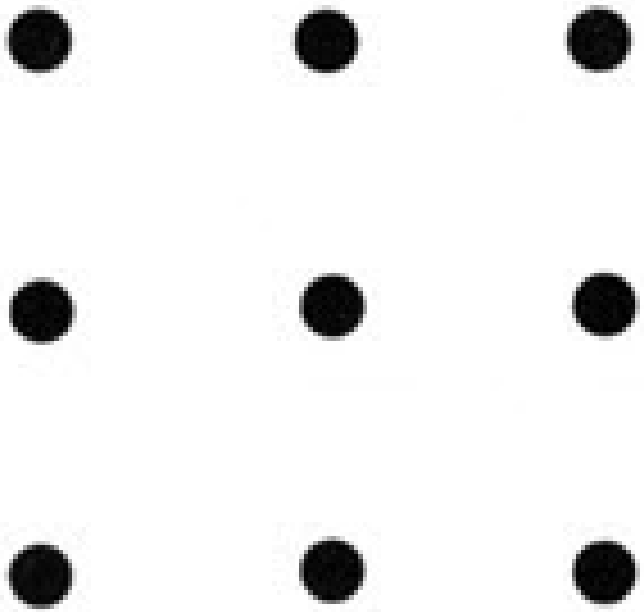
Coyle MG. Journal of Pediatrics 2002;140:561–4

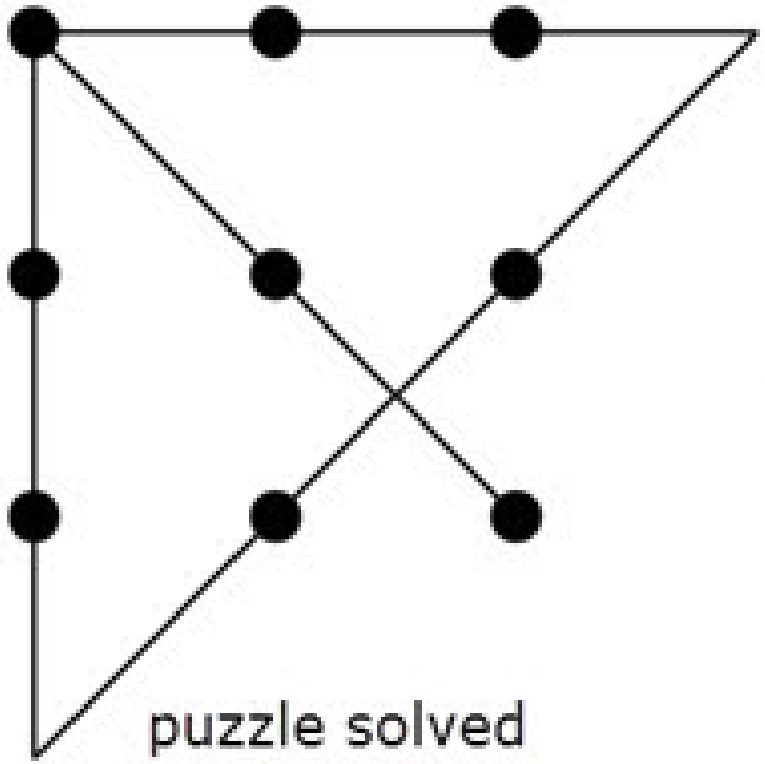

Source: http://www.projectknow.com
500ml
Methadone Hydrochloride DTF 1mg/1ml Oral Solution
central nervous system
MS Brown et al. Journal of Perinatology 2014; (1-6)

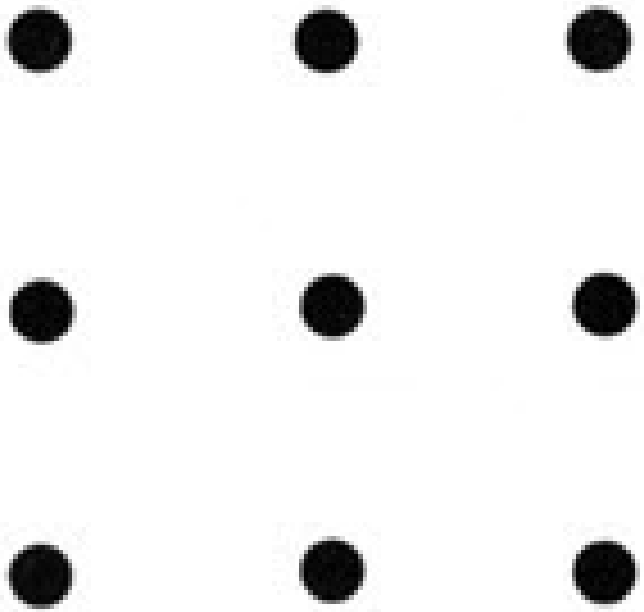
Agthe, et al. Pediatrics 2009;123:e849–56.

Standard Approach

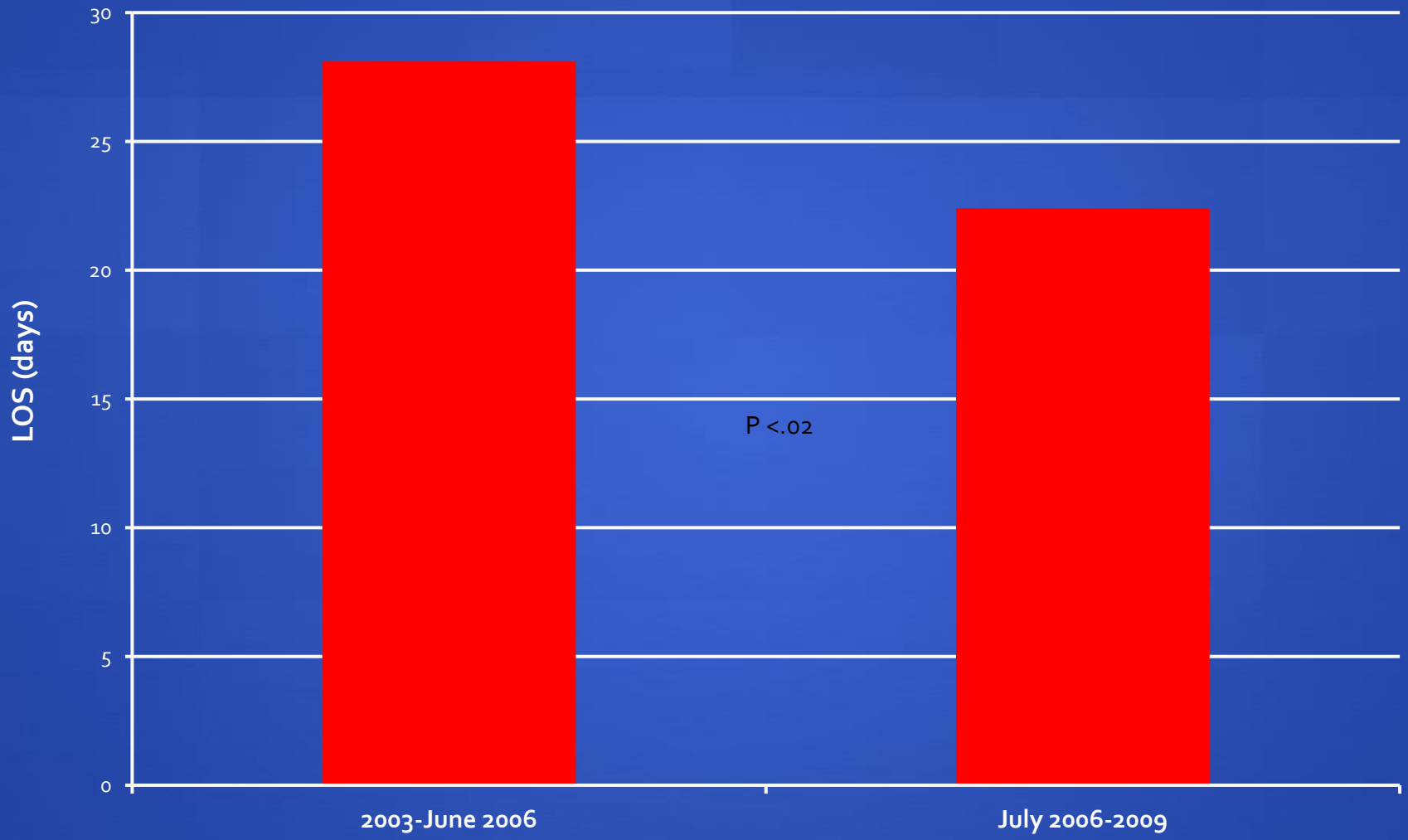
- Medications
- NICU
- Finnegan Scores
- Medication Dosing
- Staff cares for the baby




puzzle solved



Length of Stay: Methadone-Exposed Infants



Yale-New Haven Children's Hospital

Medication Studies

- DTO vs. DTO plus clonidine: 17 days vs. 12 days
- Morphine vs. Phenobarbitone: 8 days vs. 12 days
- Morphine vs. DTO 30 days vs. 27 days
- DTO vs. DTO plus Phenobarbitone 79 days vs. 38days
- Methadone vs. Morphine 17 days vs. 24 days

neonatal withdrawal signs. Clinicians have used discrete or serial scores to assist with therapeutic decisions. The Lipsitz tool, also known as the Neonatal Drug Withdrawal Scoring System,[76] was recommended in the 1998 American Academy of Pediatrics statement "Neonatal Drug Withdrawal,"[100] probably because it is a relatively simple metric with good sensitivity for identifying clinically important withdrawal. The modified Neonatal Abstinence Scoring System (Fig 1),[101] is the predominant tool used in the United States.[102] This more comprehensive instrument assigns a cumulative score based on the interval observation of 21 items relating to signs of neonatal withdrawal.[103] In 1 study, administration of this scoring system with infants verified not to have been exposed to prenatal opiates by meconium analysis resulted in a stable median score of 2 during each of the first 3 days of life, with 95th percentile scores of 5.5 and 7 on days 1 and 2, respectively.[104]

Infants at risk for NAS should be carefully monitored in the hospital for the development of signs consistent with withdrawal. The appropriate duration of hospital observation is variable and depends on a careful assessment of the maternal drug history. An infant born to a mother on a low-dose prescription opiate with a short half-life (eg, hydrocodone; average half-life, 4 hours) may be safely discharged if there are no signs of withdrawal by 3 days of age, whereas an infant born to a mother on an opiate with a prolonged half-life (eg, methadone) should be observed for a minimum of 5 to 7 days. Initial treatment of infants who develop early signs of withdrawal is directed at minimizing environmental stimuli (both light and sound) by placing the infant in a dark, quiet environment; avoiding autostimulation by careful swaddling; responding early to an infant's signals; adopting appropriate infant positioning and comforting techniques (swaying, rocking); and providing frequent small volumes of hypercaloric formula or human milk to minimize hunger and allow for adequate growth. Caloric needs may be as high as 150 to 250 cal/kg per day because of increased energy expenditure and loss of calories from regurgitation, vomiting, and/or loose stools.[105,106] The infant needs to be carefully observed to recognize fever, dehydration, or weight loss promptly. The goals of therapy are to ensure that the infant achieves adequate sleep and nutrition to establish a consistent pattern of weight gain and begins to integrate into a social environment. Maternal screening for comorbidities, such as HIV or hepatitis C virus infections and polydrug abuse, needs to be performed. Additional supportive care in the form of intravenous fluids, replacement electrolytes, and gavage feedings may be necessary to stabilize the infant's condition in the acute phase and obviate the need for pharmacologic intervention. When possible, and if not otherwise contraindicated, mothers who adhere to a supervised drug treatment program should be encouraged to breastfeed so long as the infant continues to gain weight. Breastfeeding or the feeding of human milk has been associated with less severe NAS that presents later and less frequently requires pharmacologic intervention.[107,108] Methadone is present in very low concentrations in human milk. Cumulative daily intake of methadone in fully breastfed infants has been estimated to range from 0.01 to 0.15 mg/day in the first 30 days of life[109] and 0.15 to 0.30 mg/day between 30 and 180 days of age.[110] Similarly, the amount of buprenorphine excreted in human milk is small. Although more information is needed to evaluate long-term neurodevelopmental outcome of infants exposed to small quantities of buprenorphine, there is no clear reason to discourage breastfeeding in mothers who adhere to methadone or buprenorphine maintenance treatment.[111]

Each nursery should adopt a protocol for the evaluation and management of neonatal withdrawal, and staff should be trained in the correct use of an abstinence assessment tool. In a recent survey of accredited US neonatology fellowship programs, only 55% had implemented a written NAS protocol, and only 69% used a published abstinence scoring system.[102]

RATIONALE AND COMPARATIVE EVIDENCE FOR PHARMACOLOGIC TREATMENT

Drug therapy is indicated to relieve moderate to severe signs of NAS and to prevent complications such as fever, weight loss, and seizures if an infant does not respond to a committed program of nonpharmacologic support. Since the introduction of the abstinence scales in 1975, published reports have documented that the decision to initiate pharmacologic treatment has been based on single or serial withdrawal scores. However, no studies to date have compared the use of different withdrawal score thresholds for initiating pharmacologic intervention on short-term outcomes (eg, severity and duration of withdrawal signs, weight gain, duration of hospitalization, need for pharmacologic treatment, or cumulative drug exposure). Withdrawal from opioids or sedative-hypnotic drugs may be life-threatening, but ultimately, drug withdrawal is a self-limited process. Unnecessary pharmacologic treatment will prolong drug exposure and the duration of hospitalization to the possible detriment of maternal-infant bonding. The only clearly defined benefit of pharmacologic treatment is the short-term amelioration of clinical signs. Studies have not addressed whether long-term morbidity related to neonatal drug withdrawal is decreased by pharmacologic management of affected infants, or whether continued postnatal drug exposure augments the risk of neurobehavioral and other morbidities. It is possible that pharmacologic therapy of the infant may introduce or reinforce a maternal disposition to rely on drugs for the treatment of infant discomfort or annoying behavior.[112]

Clinicians have treated NAS with a variety of drug preparations, including opioids (tincture of opium, neonatal morphine solution, methadone, and paregoric), barbiturates (phenobarbital), benzodiazepines (diazepam, lorazepam), clonidine, and phenothiazines (chlorpromazine). Information pertinent to the use of these drug preparations in infants is well summarized in the previous American Academy of Pediatrics statement.[100] Recent surveys have documented that, in accord with the recommendations of that statement, 94% of UK and 83% of US clinicians use an opioid (morphine or methadone) as the drug of first choice. The majority of practitioners use phenobarbital as a second drug if the opiate does not adequately control withdrawal signs.[102,113] Daily doses of morphine ranged from 0.24 mg/kg per day to 1.3 mg/kg per day.[113] Paregoric is no longer used, because it contains variable concentrations of other opioids, as well as toxic ingredients such as camphor, anise oil, alcohol, and benzoic acid.[100] The use of diazepam has also fallen into disfavor because of a documented lack of efficacy compared with other agents and because of its adverse effects on infant suck and swallow reflexes.[114–116]

Meta-analyses of published trials regarding the pharmacologic treatment of neonatal withdrawal are available.[117,118] In 2 Cochrane meta-analyses, either an opioid[117] or a sedative[118] drug treatment

NEONATAL ABSTINENCE SCORING SYSTEM

SYSTEM	SIGNS AND SYMPTOMS	SCORE													COMMENTS
CENTRAL NERVOUS SYSTEM DISTURBANCES	Continuous High Pitched (or other) Cry	2													Daily Weight:
	Continuous High Pitched (or other) Cry	3													
	Sleeps <1 Hour After Feeding	3													
	Sleeps <2 Hours After Feeding	2													
	Sleeps <3 Hours After Feeding	1													
	Hyperactive Moro Reflex	2													
	Markedly Hyperactive Moro Reflex	3													
	Mild Tremors Disturbed	1													
	Moderate-Severe Tremors Disturbed	2													
	Mild Tremors Undisturbed	3													
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	Excoriation (Specific Area)	1													
	Myoclonic Jerks	3													
	Generalized Convulsions	5													
METABOLIC/VASOMOTOR/RESPIRATORY DISTURBANCES	Sweating	1													
	Fever 100.4°-101°F (38°-38.3°C)	1													
	Fever > 101°F (38.3°C)	2													
	Frequent Yawning (>3-4 times/interval)	1													
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	Nasal Stuffiness	1													
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GASTRO-INTESTINAL DISTURBANCES	Excessive Sucking	1													
	Poor Feeding	2													
	Regurgitation	2													
	Projectile Vomiting	3													
	Loose Stools	2													
	Watery Stools	3													
TOTAL SCORE															
INITIALS OF SCORER															

FIGURE 1
Modified Finnegan's Neonatal Abstinence Scoring Tool. Adapted from ref 101.

adopting appropriate infant positioning and comforting techniques (swaying, rocking); and providing frequent small volumes of hypercaloric formula or human milk to minimize hunger and allow for adequate growth. Caloric needs may be as high as 150 to 250 cal/kg per day because of increased energy expenditure and loss of calories from regurgitation, vomiting, and/or loose stools.[105,106] The infant needs to be carefully observed to recognize fever, dehydration, or weight loss promptly. The goals of therapy are to ensure that the infant achieves adequate sleep and nutrition to establish a consistent pattern of weight gain and begins to integrate into a social environment. Maternal screening for comorbidities, such as HIV or hepatitis C virus infections and polydrug abuse, needs to be performed. Additional supportive care in the form of intravenous fluids, replacement electrolytes, and gavage feedings may be necessary to stabilize the infant's condition in the acute phase and obviate the need for pharmacologic intervention. When possible, and if not otherwise contraindicated, mothers who adhere to a supervised drug treatment program should be encouraged to breastfeed so long as the infant continues to gain weight. Breastfeeding or the feeding of human milk has been associated with less severe NAS that presents later and less frequently requires pharmacologic intervention.[107,108] Methadone is present in very low concentrations in human milk. Cumulative daily intake of methadone in fully breastfed infants has been estimated to range from 0.01 to 0.15 mg/day in the first 30 days of life[109] and 0.15 to 0.30 mg/day between 30 and 180 days of age.[110] Similarly, the amount of buprenorphine excreted in human milk is small. Although more information is needed to evaluate long-term neurodevelopmental outcome of infants exposed to small quantities of buprenorphine, there is no clear reason to discourage breastfeeding in mothers who adhere to methadone or buprenorphine maintenance treatment.[111]

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Meta-analyses of published trials regarding the pharmacologic treatment of neonatal withdrawal are available.[117,118] In 2 Cochrane meta-analyses, either an opioid[117] or a sedative[118] drug treatment was compared with a control treatment that could include a nonpharmacologic intervention, a placebo treatment, or another opioid and/or sedative drug. The authors prospectively designated 4 primary outcomes (failure of treatment to control withdrawal signs; incidence of seizures; survival; and neurodevelopmental outcome) for meta-analysis. Treatment failure was defined variously as the inability of the treatment to maintain abstinence scores within a preset "safe" level and/or the need to add another drug therapy. Some studies did not report primary outcomes and instead quantified secondary outcomes (eg, duration of treatment, duration of hospitalization, rate of weight gain, etc).

Seven studies of opioid treatment that enrolled a total of 585 infants were identified between 1983 and 2004. Methodologic flaws were common and included quasirandom patient allocation; substantial and often unexplained differences in allocation of patients to treatment groups; imbalances in group characteristics after randomization; failure to mask study treatments; and failure to mask outcome measurements. In the single study that assessed oral morphine treatment versus supportive therapy only, 3 consecutive Finnegan scores ≥8 prompted institution of the intervention.[119] No significant effect of morphine was found on the rate of treatment failure. Oral morphine significantly increased the duration of treatment and the length of hospital stay, but it did reduce the number of days required to regain birth weight and duration of supportive care. Four studies compared treatment failures of opioids (paregoric, oral morphine, or methadone) with phenobarbitone.[8,119–121] Neither the meta-analysis nor any individual study identified a significant difference in treatment failure. One study reported a lower incidence of seizures in the opioid (paregoric) treatment group.[122] No consistent trends in secondary outcomes were observed, although 1 study reported a shorter duration of therapy in the phenobarbitone compared with the paregoric treatment group,[123] and another made the opposite observation when the opioid used was oral morphine.[121] Three studies individually and in combination reported significantly lower rates of treatment failure in infants assigned to opioid (paregoric or methadone) compared with diazepam therapy[8,114,120] but did not define differences in secondary outcomes. No studies reported mortality or neurodevelopmental outcomes.

A second Cochrane review analyzed 6 trials involving 305 infants published between 1969 and 2002 in which sedative treatment of NAS was compared with a nonopioid therapy. Methodologic concerns were similar to the opioid treatment trials. In the sole study of phenobarbitone versus supportive care, no difference in treatment failure was found, but treatment significantly increased the duration of therapy and hospital stay.[119] A small study that allocated infants already treated with diluted tincture of opium (DTO) to phenobarbitone as a second drug versus no additional treatment identified no infants in either group with treatment failure but observed significant reductions in the duration of hospitalization (38 vs 79 days) and the maximal daily dose of opioid in the phenobarbitone-treated infants.[124] Infants were discharged from the hospital once they were no longer taking opioids. However, the mean duration of phenobarbitone treatment was 3.5 months. Of 3 studies that compared phenobarbitone and diazepam treatment, 1 found a significantly lower rate of treatment failure in the phenobarbitone group.[8,114,120] One study of phenobarbitone versus chlorpromazine[125] found no differences in primary or secondary outcomes.

Since 2004, a number of small studies of varying methodologic quality have compared pharmacologic treatments. In a prospective randomized double-masked study, Langenfeld et al[126] could not identify differences in duration of treatment, duration of hospitalization, or in weight gain (g/day) in infants treated with either DTO or oral morphine drops. A retrospective study found no difference in length of hospitalization in infants with NAS who were treated with methadone or oral morphine solution, but did correlate higher maternal methadone doses with longer lengths of stay.[127] Ebner et al[128] examined the incidence of NAS in infants born to mothers maintained with methadone, morphine, or buprenorphine and compared phenobarbital and oral morphine treatments in affected infants. Sixty-eight percent of infants born to mothers maintained on methadone required pharmacologic treatment at a mean age of 58 hours, compared with 82% of infants at a mean age of 33 hours in the morphine group and 21% of infants at a mean age of 34 hours in the buprenorphine group. The duration of treatment was significantly shorter for infants who received morphine compared with infants who were treated with phenobarbital. A randomized comparison trial of sublingual buprenorphine versus neonatal opium solution for the treatment of NAS showed a nonsignificant reduction in length of treatment and duration of hospitalization in the buprenorphine group.[129] Buprenorphine therapy was well tolerated.

Clonidine is an α_2-adrenergic receptor agonist that has been used in combination with an opioid or other drug in older children and adults to reduce withdrawal symptoms.[130,131] Via a negative feedback mechanism, clonidine

reduces CNS sympathetic outflow and palliates symptoms of autonomic overactivity such as tachycardia, hypertension, diaphoresis, restlessness, and diarrhea. Cessation of clonidine treatment can result in a rebound of autonomic activity. Reported experience with clonidine as a primary or adjunctive treatment of NAS is limited but promising. In a small case series, 6 of 7 infants with NAS showed significant resolution of signs when treated with oral clonidine.[132] In a randomized double-masked controlled trial, Agthe et al[133] compared the efficacy and safety of treating NAS with DTO plus oral clonidine (1 μg/kg every 3 hours) versus DTO plus placebo in 80 infants with prenatal exposure to methadone and/or heroin. The combination therapy significantly reduced the median length of treatment of all infants and for infants exposed to methadone, but more infants in the DTO/clonidine group required resumption of DTO after initial discontinuation. The mean total dose of morphine over the treatment course was ~60% lower in the combination therapy group. No clinically significant differences in feeding, weight gain or loss, heart rate, or blood pressure were observed. In another case series, oral clonidine was administered either as a primary or adjunctive therapy for the prevention or treatment of narcotic withdrawal in infants on intravenous fentanyl or infants with antenatal exposure to opiates.[134] In all cases, treatment was successful and clonidine was discontinued without sequelae after a mean duration of 7 days. In a retrospective case series, infants who had evidence of NAS attributable to antenatal methadone exposure had lower severity scores and required fewer days of drug therapy and hospitalization if they had been treated with a combination of clonidine and chloral hydrate rather than a combination of morphine and phenobarbital.[135]

A recently published case series from France that used a historical cohort for a comparison has suggested that the treatment of NAS with the phenothiazine, chlorpromazine, as a single drug may be more effective than treatment with morphine.[136] Infants treated with oral morphine had significantly longer median durations of treatment and hospitalization in comparison with infants treated with chlorpromazine. No adverse affects were reported.

OUTCOME

Assessment of potential long-term morbidity specifically attributable to neonatal drug withdrawal and its treatment is difficult to evaluate. Few studies have followed drug-exposed children beyond the first few years of life. Confounding variables, such as environment and dysfunctional caregivers, complicates the interpretation of outcomes. In a small study, developmental scores on the mental index on the Bayley Scales of Infant Development were not affected by the severity of withdrawal or the treatment chosen.[114] Mean scores on the Bayley Scales of Infant Development were similar for all infants treated for withdrawal, including those receiving phenobarbital, paregoric, or a combination therapy. Scores of infants whose withdrawal was too mild to qualify for pharmacologic intervention were also similar.

Fourteen drug-exposed infants with withdrawal-associated seizures were reported by Doberczak et al.[25] The abstinence scores for 5 of these infants were <7 (the cutoff for treatment); hence, they received no pharmacologic therapy before the onset of seizures. Thirteen of the 14 infants were offspring of mothers enrolled in a methadone treatment program; however, the success of maternal treatment was not described. Of the 14 infants with seizures, 12 were available for evaluation at 1 year of age; results of neurologic examinations were normal in 9 of the 12 infants evaluated. EEG results were abnormal in 9 neonates; however, subsequent EEGs for 7 of 8 of these infants normalized during follow-up. Mean scores on the Bayley Scales of Infant Development were also normal by 1 year of age, similar to matched controls that were drug exposed, but in whom withdrawal-associated seizures did not develop.[24] Withdrawal-associated seizures seem to be primarily myoclonic, to respond to opiates, and to carry no increased risk of poor outcome. Withdrawal-associated seizures in neonates are different from those associated with other causes. Based on the depression of norepinephrine and dopamine observed with methadone exposure in animal models, withdrawal seizures are speculated to be attributable to lowered levels of neurotransmitters.[157,158] The normalization of the EEG and normal neurologic development are believed to reflect recovery of normal neurotransmitter concentrations during early infancy. Bandstra et al[139] have comprehensively reviewed outcomes of infants and toddlers who were exposed prenatally to opioids and cocaine.

MANAGEMENT OF ACQUIRED OPIOID AND BENZODIAZEPINE DEPENDENCY

One of the cornerstones in caring for critically ill children is to provide adequate and safe analgesia, sedation, amnesia, and anxiolysis by using both pharmacologic and nonpharmacologic measures. Pharmacologic treatment typically includes medications in the opioid and benzodiazepine drug classes. However, if these drugs cannot safely be discontinued within a few days, physical dependence on 1 or both of these classes of medication can develop and manifest with signs and symptoms of withdrawal on acute dosage reduction or cessation of therapy. Infants who undergo complex surgery, who require prolonged medical intensive care for conditions such as respiratory failure or persistent pulmonary hypertension, or who are supported with extracorporeal membrane oxygenation (ECMO) therapy are among those at greatest risk of acquired drug dependency.

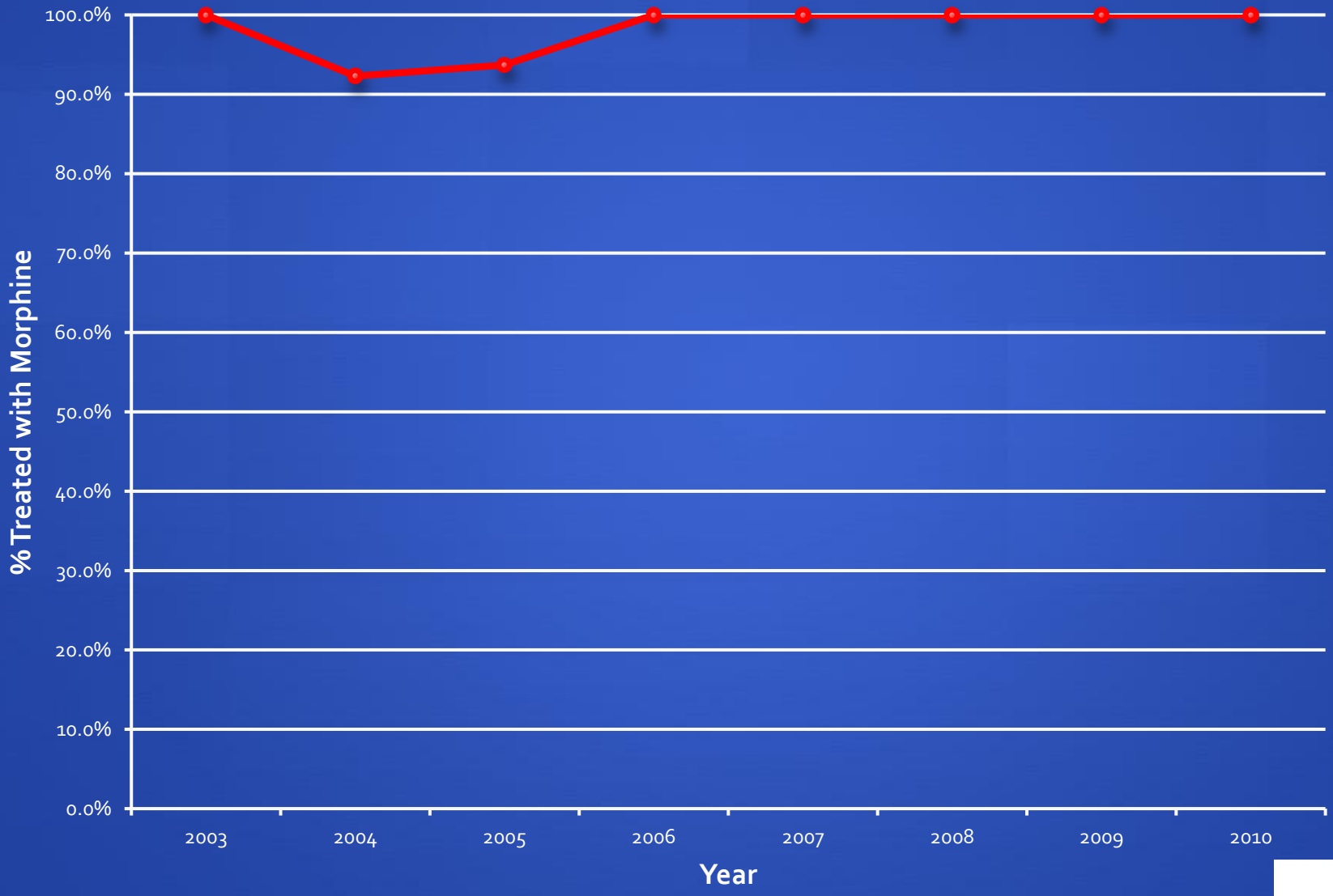
Extended treatment with opioids via continuous intravenous infusion results in drug tolerance. Even short-term opioid exposure alters the number and affinity of receptors in key neuronal centers so that an escalation of the opioid infusion rate (which produces an increase in opioid plasma concentrations) becomes necessary to achieve the same physiologic effect.[140] By itself, the development of tolerance does not predict physical dependency or withdrawal.[141] Cumulative exposure to fentanyl, quantified by the total dose in milligrams per kilogram or the number of consecutive days of treatment, correlated with the likelihood of withdrawal.[140,142,143] By using a multiple logistic regression analysis, Arnold et al[140] found that the duration of ECMO therapy was an even more powerful predictor of withdrawal than was cumulative fentanyl exposure. Katz et al[142] reported that among 23 mechanically ventilated children aged 1 week to 22 months (mean, 6 months) who were treated for >24 hours with a continuous fentanyl infusion, 13 of 23 children (57%) developed withdrawal as defined by a Finnegan score ≥8. In this prospective study, a cumulative fentanyl exposure in excess of 2.5 mg/kg or 9 days of therapy was 100% predictive of withdrawal. More recently, in a prospective study of 19 neonates treated with fentanyl for a minimum of 24 hours, Dominquez et al[143] documented that a cumulative fentanyl dose ≥415 μg/kg predicted withdrawal with 70% sensitivity and 78% specificity and that an infusion duration ≥8 days was 90% sensitive and 67% specific for withdrawal. In adults, concomitant treatment with neuromuscular paralytic agents or propofol for >24 hours also increased the likelihood of withdrawal.[144] Signs and symptoms of withdrawal from fentanyl commence within 24 hours of cessation of therapy.

The refinement of pain management in children over the past 2 decades has witnessed an expansion of the use of opioids in the intensive care setting. As a result, more children have been treated for actual or potential withdrawal symptoms as a comorbidity of hospitalization. Fentanyl, a pure μ-opioid receptor antagonist, has become the opioid of choice because of its rapid onset of action, short duration of effect (half-life of 0.5–1 hour), excellent potency, and minimal acute adverse effects. However, fentanyl has not been demonstrated to be safer or more effective than morphine for the provision of long-term analgesia. Indeed, 1 study has reported that patients who were treated prospectively with a continuous morphine infusion during ECMO experienced a significantly lower need for supplemental analgesia, a lower rate of dependency, and a shorter hospital stay compared with a previous group of patients treated with fentanyl during ECMO.[145]

Practitioners have employed a variety of strategies to treat or, in high-risk patients, to prevent signs and symptoms of opioid withdrawal in infants and children. Carr and Todres[146] reported success with a gradual taper of the opioid infusion rate. Children who had received continuous opioid infusions for more than a week required 2 to 3 weeks for complete weaning. One disadvantage of this approach was that intravenous access had to be maintained for the entire course of treatment. Tobias et al[147] were among the first investigators to describe treatment of opioid withdrawal by conversion to enteral methadone. Methadone was chosen as the opioid of choice because of its excellent oral bioavailability (70%–100%) and long half-life (19–41 hours), which allowed for long intervals between doses.[148] In this initial report, 3 symptomatic patients who had been exposed to continuous or bolus opioids for up to 7 weeks were transitioned to a methadone regimen of 0.1 mg/kg, orally, every 12 hours. Dose reduction by 10% to 20% of the initial dose per week resulted in successful weaning in 4 to 6 weeks.

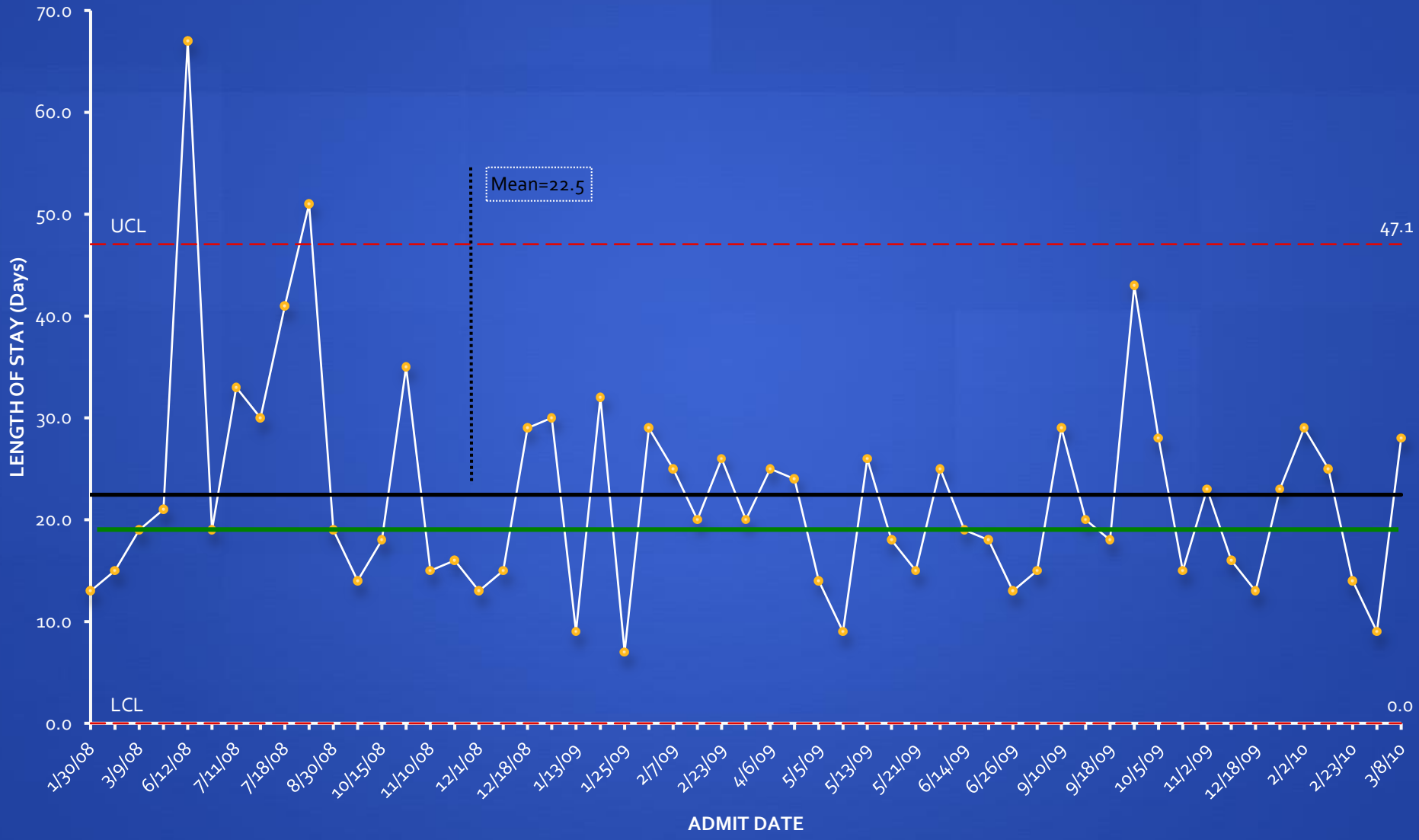
In 2000, Robertson and et al[149] reported the outcomes of 10 children 6 months to 18 years of age who had received >7 days of opioids (range, 7–53 days). An amount of methadone, equipotent to the existing daily fentanyl or morphine dose, was determined. This amount was reduced by a factor of 6 because of the longer half-life of methadone to calculate the initial total daily methadone dose. Protocols specified 2 different weaning schedules, depending on whether the patient had been treated with opioids (fentanyl or morphine) for either 7 to 14 days or for >14 days. Treatment intervals were gradually lengthened from every 6 hours to every 24 hours when methadone was discontinued. Outcomes of these patients were compared with recent control patients who had also been treated with enteral methadone but not under a standard protocol. Among the protocol patients, there were no treatment failures. Weaning was accomplished in a median of 9 days (range, 5–10 days), which was significantly less than the median of 20 days (range, 9–31 days) observed in the nonprotocol children. Concurrent use of benzodiazepines occurred in 6 of the protocol children, compared

Percent of NAS Patients Treated with Morphine



YALE-NEW HAVEN CHILDREN'S HOSPITAL

Length of Stay: Methadone exposed infants



The standard approach: why?

- Medications