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CLINICAL REPORT

Neonatal Drug Withdrawal

abstract

Maternal use of certain drugs during pregnancy can result in transient neonatal signs consistent with withdrawal or acute toxicity or cause sustained signs consistent with a lasting drug effect. In addition, hospitalized infants who are treated with opioids or benzodiazepines to provide analgesia or sedation may be at risk for manifesting signs of withdrawal. This statement updates information about the clinical presentation of infants exposed to intrauterine drugs and the therapeutic options for treatment of withdrawal and is expanded to include evidence-based approaches to the management of the hospitalized infant who requires weaning from analgesics or sedatives. *Pediatrics* 2012;129:e540–e560

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KEY WORDS

opioid, methadone, heroin, fentanyl, benzodiazepine, cocaine, methamphetamine, SSRI, drug withdrawal, neonate, abstinence syndrome

ABBREVIATIONS

CNS—central nervous system
DTO—diluted tincture of opium
ECMO—extracorporeal membrane oxygenation
FDA—Food and Drug Administration
5-HIAA—5-hydroxyindoleacetic acid
ICD-9—International Classification of Diseases, Ninth Revision
NAS—neonatal abstinence syndrome
SSRI—selective serotonin reuptake inhibitor

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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INTRODUCTION

Use and abuse of drugs, alcohol, and tobacco contribute significantly to the health burden of society. The 2009 National Survey on Drug Use and Health reported that recent (within the past month) use of illicit drugs, binge or heavy alcohol ingestion, and use of tobacco products occurred in 8.7%, 23.7%, and 27.7%, respectively, of the population 12 years or older.[1] Numerous case reports have documented the use of a variety of drugs by women of childbearing age (Table 1). Intrauterine exposure to certain drugs may cause congenital anomalies and/or fetal growth restriction, increase the risk of preterm birth, produce signs of withdrawal or toxicity in the neonate, or impair normal neurodevelopment.[2] Fetal exposure to marijuana, the illicit drug most commonly used by pregnant women, does not cause clinically important neonatal withdrawal signs but may have subtle effects on long-term neurobehavioral outcomes.[3] With the use of computer-assisted interviewing techniques that preserved confidentiality, the 2009 National Survey on Drug Use and Health noted that 4.5% of pregnant women 15 to 44 years of age reported recent use of illicit drugs (eg, marijuana, cocaine, hallucinogens, heroin, methamphetamines, and nonmedical use of prescription drugs). Binge or heavy drinking in the first trimester was reported by 11.9%, and recent tobacco use was reported by 15.3%. Rates of recent illicit drug use and smoking were lower among pregnant compared with nonpregnant women across all age groups, except for those 15 to 17 years of age. In the latter age group, the rates of illicit drug use and smoking were higher among those who were pregnant compared with those who were not pregnant (15.8% vs 13.0% and 20.6% vs 13.9%, respectively). The reported rates of illicit drug use most likely underestimate true rates, because the percentage of pregnant women who report the recent use of illicit drugs on screening interviews can

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TABLE 1 Major Drugs of Abuse[a]

Opioids	CNS Stimulants	CNS Depressants	Hallucinogens
Agonists	Amphetamines	Alcohol	Indolealkylamines (LSD, psilocin, psilocybin, DMT, DET)
Morphine	Dextroamphetamine (Dexedrine)	Barbiturates	Phenylethylamines (mescaline, peyote)
Codeine	Methamphetamine	Benzodiazepines	Phenylisopropylamines (MDA, MMDA, MDMA, MDEA)
Methadone	Amphetamine sulfate	Other sedative-hypnotics	Inhalants
Meperidine (Demerol)	Amphetamine congeners	Methaqualone (Quaalude)	Solvents and aerosols (glues, gasoline, paint thinner, cleaning solutions, nail polish remover, Freon)
Oxycodone (Percodan, OxylR, Percolone, Roxicodone, Percocet, OxyContin)	Benzphetamine (Didrex)	Glutethimide (Doriden)	Nitrites
Propoxyphene (Darvon)	Diethylpropion (Tenuate)	Chloral hydrate	Nitrous oxide
Hydromorphone (Dilaudid)	Fenfluramine	Cannabinoids	
Hydrocodone (Lortab, Vicodin)	Phendimetrazine (Adipost, Bontril, Prelu-2)	Marijuana	
Fentanyl (Sublimaze)	Phentermine (Adipex-P, Zantryl)	Hashish	
Tramadol (Ultram, Ultracet)	Cocaine		
Heroin	Methylphenidate (Ritalin, Concerta)		
Antagonists	Pemoline (Cylert)		
Naloxone (Narcan)	Phenylpropanolamine		
Naltrexone (ReVia)	Phencyclidines		
Mixed Agonist-Antagonists	Nicotine		
Pentazocine (Talwin)			
Buprenorphine (Buprenex)			

DET, diethyltryptamine; DMT, dimethyltryptamine; LSD, lysergic acid diethylamide; MDA, methylenedioxyamphetamine; MDEA, 3,4-methylenedioxyethamphetamine; MDMA, 3,4-methylenedioxymethamphetamine (ecstasy); and MMDA, 3-methoxy-4,5-methylenedioxyamphetamine.
[a] Adapted from Milhorn.[160]

be substantially lower than that determined by drug screening using biological samples. For infants, the use of *International Classification of Diseases, Ninth Revision* (*ICD-9*)-based hospital discharge databases to determine the incidence of neonatal drug withdrawal secondary to intrauterine exposure has in the past underestimated the incidence of this condition.[4] Data compiled by the Agency for Healthcare Research and Quality and by the Florida Department of Health attest to an increased incidence and/or recognition of neonatal withdrawal syndrome (ICD-9 code 779.5). Nationally, the number of infants coded at discharge with neonatal withdrawal increased from 7653 in 1995 to 11 937 in 2008. In Florida, the number of newborns discharged with ICD-9 code 779.5 climbed by more than 10-fold, from 0.4 to 4.4 discharges per 1000 live births, from 1995 to 2009. An indeterminate part of these observed increases has resulted from more liberal use of prescription opiates in pregnant women to palliate a wide variety of etiologies of acute or chronic pain. In a recent report, chronic use of narcotic prescriptions (use for ≥1 intrapartum month) among pregnant women cared for at a single clinic increased fivefold from 1998 to 2008, and 5.6% of infants delivered to these women manifested signs of neonatal withdrawal.[5]

Signs characteristic of neonatal withdrawal have been attributed to intrauterine exposure to a variety of drugs (Table 2). Other drugs cause signs in neonates because of acute toxicity. Chronic in utero exposure to a drug (eg, alcohol) can lead to permanent phenotypical and/or neurodevelopmental-behavioral abnormalities consistent with drug effect. Signs and symptoms of withdrawal worsen as drug levels decrease, whereas signs and symptoms of acute toxicity abate with drug elimination. Clinically important neonatal withdrawal most commonly results from intrauterine opioid exposure. The constellation of clinical findings associated with opioid withdrawal has been termed the neonatal abstinence syndrome (NAS). Among neonates exposed to opioids in utero, withdrawal signs will develop in 55% to 94%.[6–9] Neonatal withdrawal signs have also been described in infants exposed antenatally to benzodiazepines,[10,11] barbiturates,[12,13] and alcohol.[14,15]

COCAINE AND OTHER STIMULANTS

An abstinence syndrome after intrauterine exposure to central nervous system (CNS) stimulants such as cocaine and amphetamine has not been clearly defined. Many studies that have assessed behavior and neurologic signs in cocaine-exposed infants have used scoring systems that were designed to evaluate opioid withdrawal. Neurobehavioral abnormalities[16,17] frequently occur in neonates with intrauterine cocaine exposure, most frequently on the second or third postnatal days.[18] These abnormalities may include irritability, hyperactivity, tremors, high-pitched cry, and excessive sucking. Because cocaine or its metabolites may be detected in neonatal urine

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TABLE 2 Maternal Nonnarcotic Drugs That Cause Neonatal Psychomotor Behavior Consistent With Withdrawal

Drug	Signs	Onset of Signs	Duration of Signs[a]	Ref. No.
Alcohol	Hyperactivity, crying, irritability, poor suck, tremors, seizures; onset of signs at birth, poor sleeping pattern, hyperphagia, diaphoresis	3–12 h	18 mo	14,15
Barbiturates	Irritability, severe tremors, hyperacusis, excessive crying, vasomotor instability, diarrhea, restlessness, increased tone, hyperphagia, vomiting, disturbed sleep; onset first 24 h of life or as late as 10–14 d of age	1–14 d	4-6 mo with prescription	12,13
Caffeine	Jitteriness, vomiting, bradycardia, tachypnea	At birth	1-7 d	161
Chlordiazepoxide	Irritability, tremors; signs may start at 21 d	Days–weeks	9 mo; 11/2 mo with prescription	11
Clomipramine	Hypothermia, cyanosis, tremors; onset 12 h of age		4 d with prescription	162
Diazepam	Hypotonia, poor suck, hypothermia, apnea, hypertonia, hyperreflexia, tremors, vomiting, hyperactivity, tachypnea (mother receiving multiple drug therapy)	Hours–weeks	8 mo; 10–66 d with prescription	10
Ethchlorvynol	Lethargy, jitteriness, hyperphagia, irritability, poor suck, hypotonia (mother receiving multiple drug therapy)		Possibly 10 d with prescription	163
Glutethimide	Increased tone, tremors, opisthotonos, high-pitched cry, hyperactivity, irritability, colic		6 mo	164
Hydroxyzine	Tremors, irritability, hyperactivity, jitteriness, shrill cry, myoclonic jerks, hypotonia, increased respiratory and heart rates, feeding problems, clonic movements (mother receiving multiple drug therapy)		5 wk with prescription	58
Meprobamate	Irritability, tremors, poor sleep patterns, abdominal pain		9 mo; 3 mo with prescription	165
SSRIs	Crying, irritability, tremors, poor suck, feeding difficulty, hypertonia, tachypnea, sleep disturbance, hypoglycemia, seizures	Hours–days	1–4 wk	31–33,35

[a] Prescription indicates the infant was treated with pharmacologic agents, and the natural course of the signs may have been shortened.

for as long as 7 days after delivery,[18] observed abnormalities in exposed infants may reflect drug effect rather than withdrawal. In an unmasked study, 6%, 14%, and 35% of infants exposed to cocaine only, heroin only, or cocaine plus heroin, respectively, qualified for treatment on the basis of scoring.[19] Several studies that used masked evaluators found that cocaine-exposed infants had either no[20,21] or minimal[22] withdrawal signs compared with cocaine-naïve infants (ie, those never exposed). Eyler et al[16] conducted a prospective controlled study of 3 groups of infants: 1 group had no documented exposure to cocaine by history or by maternal and infant urine testing; a second group was cocaine exposed but had negative urine screening at birth; and a third group had cocaine metabolites detected in neonatal urine. Observers masked to infant status performed assessments using the Brazelton Neonatal Behavioral Assessment Scale.[23] Infants who were positive for cocaine metabolites did not differ significantly from metabolite-negative infants with a history of exposure nor from cocaine-naïve infants. These findings supported neither a withdrawal nor a drug toxicity syndrome. Cocaine-exposed infants have been described as having a higher incidence of abnormal auditory brainstem responses and EEGs, compared with nonexposed infants.[24,25] In another study, infants with heavy exposure to cocaine had similar Brazelton findings at 2 to 3 days of age as did infants with light or no exposure; however, by 17 days of age, heavily exposed infants were more excitable and demonstrated poorer state regulation.[26] No published studies have carefully evaluated pharmacologic treatment of infants with signs attributable to prenatal cocaine exposure.

Methamphetamine abuse has been reported among pregnant women,[27] although overall rates are low compared with cocaine and appear to have decreased in the general population between 2006 and 2008.[1] Methamphetamine is an extremely potent sympathomimetic agent that induces euphoria and increases alertness and self-confidence, because it produces a massive efflux of dopamine in the CNS. Pregnant women who abuse methamphetamine are at increased risk of preterm birth, placental abruption, fetal distress, and intrauterine growth restriction at rates similar to those for pregnant women who use cocaine. In 1 study, only 4% of infants exposed to methamphetamine were treated for drug withdrawal, but it was not possible to exclude concomitant abuse of other drugs as contributory in all cases.[27] There are reports of long-term adverse neurotoxic effects of in utero methamphetamine exposure on behavior, cognitive skills, and physical dexterity.[28,29]

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Selective serotonin reuptake inhibitors (SSRIs) are a class of antidepressant medications that became available for widespread clinical use in 1988. SSRIs

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(eg, fluoxetine [Prozac], paroxetine [Paxil], sertraline [Zoloft], citalopram [Celexa], escitalopram [Lexapro], and fluvoxamine [Luvox]) are now the most frequently used drugs to treat depression both in the general population and in pregnant women.[30] Case reports,[31] adverse drug reaction reports,[32] and prospective studies[33,34] linked third-trimester use of SSRIs in pregnant women to a constellation of neonatal signs that include continuous crying, irritability, jitteriness, and/or restlessness; shivering; fever; tremors; hypertonia or rigidity; tachypnea or respiratory distress; feeding difficulty; sleep disturbance; hypoglycemia; and seizures.[35] The onset of these signs ranged from several hours to several days after birth and usually resolved within 1 to 2 weeks. In 1 infant exposed to paroxetine, signs persisted through 4 weeks of age.[36] In severely affected infants, a short-term course of chlorpromazine provided measurable relief of symptoms.[36]

Several authors have discussed whether these signs are better explained by serotonin syndrome (attributable to increased serotonin concentration in the intersynaptic cleft) or by SSRI withdrawal (attributable to a relative hyposerotonergic state).[30,32,35,37–40] In adults, treatment with a single SSRI may cause mild to moderate serotonin syndrome, but severe signs are more likely to occur when 2 or more drugs that increase serotonin concentration by different mechanisms are prescribed.[35] In adults, serotonin syndrome is characterized by the following triad of clinical signs: changes in mental status (agitation, confusion); autonomic hyperactivity (fever, tachycardia, tachypnea, diaphoresis, mydriasis); and neuromuscular abnormalities (tremor, clonus, hyperreflexia, hypertonia). On the other hand, serotonin withdrawal in adults manifests with subjective symptoms that include anxiety, headache, nausea, fatigue, low mood, and, rarely, extrapyramidal signs such as dystonia. Hence, in most cases, the clinical syndrome reported among neonates born to mothers on SSRI treatment is consistent with a gradual resolution of a hyperserotonergic condition rather than with the evolution of a hyposerotonergic state. Still, in a few cases, drug withdrawal may be a better explanation.[35]

Biochemical studies that correlate serial serum SSRI (or active metabolite) concentrations and markers of CNS serotonin activity (eg, 5-hydroxyindoleacetic acid [5-HIAA], a metabolite of serotonin) with changes in clinical signs could be helpful in differentiating toxicity from withdrawal. In adults, cerebrospinal fluid concentrations of 5-HIAA (but not serum concentrations of serotonin) correlate inversely with increased CNS serotonin activity that results from SSRI treatment. One prospective study compared concentrations of SSRI and active metabolites at birth, 2 days of life, and 2 weeks of life; cord blood monoamine and metabolite; and serial serotonergic scores in infants born to mothers on treatment with SSRIs and those of SSRI-naïve control infants.[39] The infants born to mothers on SSRIs had an average serotonergic score fourfold greater than SSRI-naïve infants. Cord blood 5-HIAA concentrations were inversely related to the initial serotonergic score, and the resolution of neonatal signs correlated with rapid declines in serially measured serum SSRI and metabolite concentrations.[39] These results do support drug toxicity rather than drug withdrawal as the cause of clinical signs. Recent authors have suggested the terms "serotonin discontinuation syndrome"[34] or "prenatal antidepressant exposure syndrome."[41]

Although 1 study reported decreased pain reactivity at 2 months of age in infants with prenatal exposure to SSRIs,[42] several recent reviews have not identified adverse neurodevelopmental outcomes among infants born to women treated with SSRIs during pregnancy.[30,34,43,44] SSRI treatment should be continued during pregnancy at the lowest effective dose, because withdrawal of medication may have harmful effects on the mother-infant dyad. Clinicians should be aware that infants are at risk for manifesting clinical signs of drug toxicity or withdrawal over the first week of life and arrange for early follow-up after the initial hospital discharge. Ideally, recommendations about lactation and breastfeeding should be made in consideration of what is known about the differences among drugs in a therapeutic class vis-à-vis the ratio of human milk to maternal plasma drug concentration, the likely total daily infant drug dose (as a fraction of the daily maternal drug dose normalized for weight), and the ratio of infant to maternal plasma drug concentration. However, in the absence of known adverse effects (eg, diminished suck, sleep disturbances, decreased growth), what constitutes an acceptable fractional drug dose or ratio of plasma concentrations is arbitrary—is 0.10 acceptable but 0.20 not? Paroxetine is the only SSRI for which the ratio of infant to maternal plasma concentrations is low and uniformly <0.10.[45] Fortinguerra et al[46] documented that paroxetine, sertraline, and fluvoxamine are minimally excreted in human milk and provide the infant <10% of the maternal daily dose (normalized for weight). Yet, Weissman et al[45] cite studies in which 6% and 33% of the reported paired infant to maternal plasma concentration ratios for sertraline and fluvoxamine, respectively, are >0.10. A mother on treatment with an SSRI who desires to nurse her infant should be counseled about the

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benefits of breastfeeding as well as the potential risk that her infant may continue to be exposed to a measureable level of the SSRI with unknown long-term effects.

OPIOIDS

Opioids are a class of natural, endogenous, and synthetic compounds that activate primarily μ-opioid (but also κ- and δ-opioid) receptors in the CNS to produce supraspinal analgesia. Other acute effects include sedation, euphoria, miosis, respiratory depression, and decreased gastrointestinal motility. Prolonged use results in physical and psychological dependence. As a class, opioids demonstrate a narrow therapeutic index. On the other hand, the interpatient range of dose necessary to achieve a similar therapeutic effect is fairly wide because of genetic differences in pharmacokinetics and pharmacodynamics.[47] Morphine is 1 of many natural opioids that can be extracted from the opium poppy. Codeine, heroin (diacetylmorphine), hydromorphone (Dilaudid), fentanyl (Sublimaze), and methadone are examples of synthetic opioids. Endogenous opioids include enkephalins, endorphins, and endomorphins. The term opiate refers to a subclass of alkaloid opioids. Methadone exerts secondary effects by acting as an *N*-methyl-D-aspartate receptor antagonist, blocking the actions of glutamate, the primary excitatory neurotransmitter in the CNS. Opioids acutely inhibit the release of noradrenaline at synaptic terminals. With chronic opioid exposure, tolerance develops as the rate of noradrenaline release over time increases toward normal. Abrupt discontinuation of exogenous opioids results in supranormal release of noradrenaline and produces the autonomic and behavioral signs and symptoms characteristic of withdrawal.

Opioid abuse in pregnant women presents additional risks for the fetus and newborn. Opioids are small lipophilic molecular weight compounds that cross placental and blood-brain barriers. Active or passive maternal detoxification is associated with increased risk of fetal distress and fetal loss. Maintenance programs with methadone (a full μ-opioid agonist and a Food and Drug Administration [FDA] schedule II controlled substance) for pregnant women can sustain opioid concentrations in the mother and fetus in ranges that minimize opioid craving, suppress abstinence symptomatology, block heroin-induced euphoria, and prevent fetal stress. Other benefits from this once controversial treatment are optimization of prenatal care and general maternal physical and mental health, as well as anticipation of potential withdrawal signs in the newborn infant. Disadvantages of methadone include the extremely unlikely achievement of successful detoxification after delivery and a more severe and prolonged course of NAS compared with heroin exposure. These issues have encouraged the development of other synthetic opioids as alternative treatments to methadone.

Subsequent to the Drug Addiction Treatment Act of 2000 that allowed office-based treatment of addiction by using FDA schedule III to V drugs, the synthetic opioid buprenorphine (a partial μ-opioid agonist) was approved by the FDA in 2002 as a schedule III controlled substance for the treatment of opioid dependence. Neither methadone nor buprenorphine is approved for use in pregnant women, and both are categorized by the FDA as class C pregnancy drugs. Nonetheless, buprenorphine, either alone (Subutex) or in combination with naloxone (Suboxone), has been used both as a first-line treatment of heroin addiction and as a replacement drug for methadone. Recent results from the Maternal Opioid Treatment: Human Experimental Research study suggest that buprenorphine has some advantages to methadone as a treatment of opioid addiction in pregnant women. Infants born to mothers treated with buprenorphine had shorter hospital stays (10 vs 17.5 days), had shorter treatment durations for NAS (4.1 vs 9.9 days), and required a lower cumulative dose of morphine (1.1 vs 10.4 mg) compared with infants born to mothers on methadone maintenance.[48]

CLINICAL PRESENTATION OF OPIOID WITHDRAWAL

The clinical presentation of NAS varies with the opioid, the maternal drug history (including timing of the most recent use of drug before delivery), maternal metabolism, net transfer of drug across the placenta, placental metabolism (W. Snodgrass, MD, PhD, personal communication, 2008), infant metabolism and excretion, and other factors. In addition, maternal use of other drugs and substances such as cocaine, barbiturates, hypnotics-sedatives, and cigarettes may influence the severity and duration of NAS. Because opioid receptors are concentrated in the CNS and the gastrointestinal tract, the predominant signs and symptoms of pure opioid withdrawal reflect CNS irritability, autonomic overreactivity, and gastrointestinal tract dysfunction (Table 3). Excess environmental stimuli and hunger will exacerbate the perceived severity of NAS.

Onset of signs attributable to neonatal withdrawal from heroin often begins within 24 hours of birth, whereas withdrawal from methadone usually commences around 24 to 72 hours of age.[49] For both opioids, evidence of withdrawal may be delayed until 5 to 7 days of age or later, which is typically after hospital discharge.[50] For

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TABLE 3 Clinical Features of the Neonatal Narcotic Abstinence Syndrome

Neurologic Excitability	Gastrointestinal Dysfunction
Tremors	Poor feeding
Irritability	Uncoordinated and constant sucking
Increased wakefulness	Vomiting
High-pitched crying	Diarrhea
Increased muscle tone	Dehydration
Hyperactive deep tendon reflexes	Poor wt gain
Exaggerated Moro reflex	Autonomic signs
Seizures	Increased sweating
Frequent yawning and sneezing	Nasal stuffiness
	Fever
	Mottling
	Temperature instability

infants exposed to buprenorphine, 1 study found that onset of withdrawal peaked at 40 hours and that signs were most severe at 70 hours of age.[51] The different time courses reflect variations in the half-lives of drug elimination. However, if 1 week or longer has elapsed between the last maternal opioid use and delivery of the infant, the incidence of neonatal withdrawal is relatively low.[52] The incidence and severity of NAS are greater in infants exposed to methadone compared with those exposed to buprenorphine[48] or heroin. Still, severe withdrawal has been described in 0 to 50% of buprenorphine-exposed infants.[53–55] In the acute phase, seizures have occurred in 2% to 11% of infants withdrawing from opioids[49,50,56]; however, abnormal EEG results without overt seizure activity have been reported in >30% of neonates.[57,58] Subacute signs of opioid withdrawal may last up to 6 months.[59]

Seizures also may be associated with withdrawal from a variety of nonnarcotic drugs (eg, barbiturates,[12,14] alcohol,[14] and sedative-hypnotics[60,61]). The mechanism and significance of seizures associated with withdrawal are unclear. Withdrawal from ethanol begins early, in general, during the first 3 to 12 hours after delivery.[12,15] Diagnosis of sedative withdrawal is more difficult, because classically it appears after the first few days of life. Barbiturate withdrawal has a median onset of 4 to 7 days, but a wide range from days 1 through 14.[12,13] Other sedative-hypnotics have exhibited even later onset, including as late as day 12 for diazepam[10] and day 21 for chlordiazepoxide.[11]

Studies of the relationship between maternal methadone dose and the incidence and severity of NAS have provided contradictory findings. Some studies demonstrated that larger maternal methadone dosages in late pregnancy were associated with greater neonatal concentrations and increased risk of withdrawal,[8,9,62–68] but others refuted a correlation.[69–74] This lack of consensus is explained in part by different approaches to the management of antenatal methadone maintenance therapy. There were substantial variations in the mean and range of daily methadone dose in the populations studied. Studies that found no correlation tended to enroll infants born to mothers who had been prescribed higher doses of methadone (50–200 mg/day), whereas those that did note a relationship between maternal dose and NAS sequelae reported lower maternal doses (eg, <50 mg/day) or included women undergoing partial detoxification.[67] Another potential explanatory factor is the significant interindividual variability in maternal methadone metabolism.[75] As a result, cumulative fetal exposure can be expected to vary among infants born to mothers on equivalent methadone regimens.

Methadone concentrations in cord blood and at 48 hours of age,[72] as well as the rate of decline in neonatal serum concentration,[65] appear to correlate with NAS signs. Kuschel et al[72] found that infants who required rescue treatment had lower cord blood methadone concentrations and that, in all but 1 infant, methadone concentrations were undetectable in the serum at 48 hours. Doberczak[65] noted that faster declines in postnatal blood methadone concentrations were associated with more severe CNS withdrawal.

Preterm Infants

Preterm infants have been described as being at lower risk of drug withdrawal with less severe and/or prolonged courses. Infants born at <35 weeks' gestation whose mothers received methadone maintenance had significantly lower total and CNS abstinence scores than did term infants of mothers receiving similar methadone dosages.[64] In a more recent study, lower gestational age correlated with a lower risk of neonatal withdrawal.[68] The apparent decreased severity of signs in preterm infants may relate to developmental immaturity of the CNS, differences in total drug exposure, or lower fat depots of drug. Alternatively, the clinical evaluation of the severity of abstinence may be more difficult in preterm infants, because scoring tools to describe withdrawal were largely developed in term or late preterm infants.[76,77] In a retrospective study, Dysart et al[78] compared the length of hospital stay, duration of medication, and cumulative medication exposure for preterm and term infants born to mothers enrolled in a methadone maintenance program. Infants were evaluated by using an abstinence scoring system[77] and treated uniformly

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with a neonatal opiate solution. All adverse outcomes were reduced in the preterm cohort.

Abuse of Multiple Drugs

The abuse of multiple drugs during pregnancy is not uncommon,[79] but its effect on the occurrence and severity of neonatal abstinence is controversial. In 1 study, abstinence scores of infants whose mothers abused cocaine and methadone were similar to the scores of infants whose mothers received high-dose maintenance methadone.[64] In another study, the neurobehavioral scores of infants exposed to intrauterine cocaine were similar to those of infants exposed to both cocaine and methadone.[80] Conversely, an unmasked study reported higher abstinence scores in infants exposed to both cocaine and heroin in comparison with those exposed to heroin or cocaine alone.[19] Infants born to mothers maintained on methadone who were also heavy smokers (>20 cigarettes per day) demonstrated higher withdrawal scores that peaked later than infants born to light smokers.[81]

A 1989 case report linked the administration of naloxone for the treatment of apnea in a baby born to a mother with recent methadone ingestion to the onset of seizures. The seizures resolved after morphine treatment but did not respond to administration of phenobarbital or diazepam.[82] For this reason, maternal use of opiates during pregnancy has remained a relative contraindication to the use of naloxone for the treatment of apnea or hypoventilation during the transition period after birth.

DIFFERENTIAL DIAGNOSIS

The presence of maternal characteristics known to be associated with drug abuse during pregnancy can be considered an indication to screen for intrauterine drug exposure. These characteristics include absent, late, or inadequate prenatal care; a previously documented or admitted history of drug abuse; a previous unexplained late fetal demise; precipitous labor; abruptio placentae; hypertensive episodes; severe mood swings; cerebrovascular accidents; myocardial infarction; and repeated spontaneous abortions.[80,83–88] The legal implications of testing and the need for consent from the mother may vary among the states.[89] Each hospital should consider adopting a policy for maternal and newborn screening to avoid discriminatory practices and to comply with local laws.

Withdrawal signs in the newborn may mimic other conditions, such as infection, hypoglycemia, hypocalcemia, hyperthyroidism, intracranial hemorrhage, hypoxic-ischemic encephalopathy, and hyperviscosity.[90] If none of these diagnoses is readily apparent, a detailed maternal drug history should be obtained that includes interviewing the mother about drug use and abuse by her partner, friends, and parents, in addition to queries about the mother's prescription and nonprescription drug use.[90,91] Because maternal self-reporting underestimates drug exposure and maternal urine screening during pregnancy fails to identify many cases of drug use,[83] appropriate neonatal drug screening should be performed. Conversely, no clinical signs should be attributed solely to drug withdrawal on the basis of a positive maternal history without a careful assessment to exclude other causes.

Screening is most commonly accomplished by using neonatal urine specimens. A urine sample must be collected as soon as possible after birth, because many drugs are rapidly metabolized and eliminated.[90,92,93] Even so, a positive urine screening result may only reflect recent drug use. Alcohol is detectable in neonatal urine for 6 to 16 hours after the last maternal ingestion. Amphetamines, benzodiazepines, cocaine metabolites, and opioids are usually cleared within 1 to 3 days after birth. Marijuana and cocaine metabolites may be detectable for weeks, depending on maternal usage.[94]

Drugs that are excreted in the hepatobiliary system as well as drugs excreted by the fetal kidneys into the amniotic fluid are concentrated in meconium. Hence, meconium analysis is most useful when the history and clinical presentation strongly suggest neonatal withdrawal, but the maternal and neonatal urine screening results are negative. Drawbacks of testing for drugs in meconium are that it is not typically performed by hospitals and that results are often not available for days to weeks. Meconium must be collected before it is contaminated by transitional, human milk, or formula stools—otherwise, the assay may not be valid or the reference laboratory may reject the sample. Assay of meconium, although not conclusive if the results are negative, is more likely to identify infants of drug-abusing mothers than is the testing of infant or maternal urine.[95,96] Other specimens that have been tested in research laboratories are maternal and neonatal hair.[97,98] Recently, testing of umbilical cord tissue by using drug class-specific immunoassays was shown to be in concordance with testing of paired meconium specimens at rates of 97%, 95%, 99%, and 91% for the detection of amphetamines, opiates, cocaine, and cannabinoids, respectively.[99] The availability of this tissue from the moment of birth (in contrast to the inherent delay in collecting urine or meconium) may foster the adoption of this method of testing.

ASSESSMENT AND NONPHARMACOLOGIC TREATMENT

Several semiobjective tools are available for quantifying the severity of

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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;

NEONATAL ABSTINENCE SCORING SYSTEM

SYSTEM	SIGNS AND SYMPTOMS	SCORE		AM						PM					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													
	Moderate-Severe Tremors Undisturbed	4													
	Increased Muscle Tone	2													
	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													
	Mottling	1													
	Nasal Stuffiness	1													
	Sneezing (>3-4 times/interval)	1													
	Nasal Flaring	2													
	Respiratory Rate >60/min	1													
	Respiratory Rate > 60/min with Retractions	2													
GASTRO-INTESTIONAL 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.

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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

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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 $\geq$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

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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.[137,138] 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

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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

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with 3 of the nonprotocol group, so that the decreased taper time on protocol was unlikely to have been confounded by other drug therapy. Weaning and discontinuation from benzodiazepines were successful during the methadone taper in all protocol patients.

Meyer et al[150] described a protocol for rescue therapy in 29 patients 1 day to 20 years of age on admission who developed withdrawal during the course of nonstandardized tapers of prolonged continuous fentanyl infusion. Withdrawal was defined as the observation of 3 consecutive Finnegan scores ≥8 obtained at 2-hour intervals. The daily fentanyl dose for the period 24 to 48 hours before withdrawal symptoms was used to calculate an equipotent dose of morphine sulfate. Morphine was administered as a bolus dose every 4 hours and titrated to effect (Finnegan score consistently <8) over 12 to 24 hours. An equipotent amount of methadone was then determined by using the effective morphine dose. Three loading doses of methadone at 12-hour intervals were administered. Afterward, doses were given every 24 hours and weaned by 10% per day. Ten patients were receiving concomitant treatment with a benzodiazepine or chloral hydrate, but these medications were not weaned during the methadone taper. Twenty-five of 29 patients successfully completed this taper over 10 days. Three patients required 21 days, and 1 patient died of sepsis. Sixteen of the patients were discharged from the hospital and completed methadone tapers on an outpatient basis. Nine of the patients had been started on clonidine during the phase of nonstandardized opioid weaning in unsuccessful attempts to prevent withdrawal. A subsequent randomized double-blind follow-up study by the same group of investigators[151] found that in a group of 37 fentanyl-treated patients, a 5-day methadone taper was as successful as the longer 10-day course (13 of 16 vs 17 of 21 [not significant]) in discontinuing opioid infusions without causing withdrawal. In contrast to their previous study, a standardized taper of lorazepam was allowed in 17 of the 37 patients while on the methadone protocol. Only 1 of these 17 patients who underwent dual tapers required rescue treatment with an increased dose of opioids.

Several factors potentially complicate the adoption of the protocols reported by Robertson, Meyer, and Berens (see Table 4) into routine neonatal clinical practices. Most obvious is that these studies were conducted in a PICU setting; few neonates were included, and their outcomes were not separately analyzed. Other investigators have emphasized that the Finnegan instrument common to all 3 studies has been validated only in term infants undergoing withdrawal secondary to in utero opioid exposure.[152,153] Therefore, the use of this tool may have underestimated withdrawal symptomatology in an older pediatric population. A third concern is that opioids and benzodiazepines are often used concurrently in the same patient, yet symptoms of opioid and benzodiazepine withdrawal overlap to a great extent. Hence, current instruments will not reliably differentiate whether withdrawal symptoms stem from relative opioid or benzodiazepine abstinence.[153] Other scales have been proposed for children and are in various stages of evaluation, including the Opioid and Benzodiazepine Withdrawal Scale,[151] the Sedation Withdrawal Score,[154] and the Sophia Benzodiazepine and Opioid Withdrawal Checklist.[155]

At this time, no optimal pharmacologic regimen for the prevention or treatment of acquired opioid and/or benzodiazepine dependency can be recommended, because the necessary comparative studies of safety and efficacy are not available.[156] Hence, it is even more incumbent on the practitioner to prescribe pharmacologic interventions with the goal of achieving the desired therapeutic effect by using the fewest drugs at the lowest doses and for the shortest durations possible.

Nonetheless, because many critically ill infants and children do receive treatment with prolonged courses of opioids and benzodiazepines, the following practices are reasonable based on the available evidence:

1. Each clinical unit can establish a threshold level of cumulative exposure to opioids and benzodiazepines above which drug dependency can be expected to occur with a likelihood that justifies anticipatory initiation of a weaning protocol. For example, setting a threshold at a cumulative fentanyl exposure of >2 mg/kg or >7 days' duration would predict a likelihood of dependency >50% but <100%.[141,142]
2. Infants with a cumulative exposure to opioids or benzodiazepines below the thresholds for initiation of weaning protocols can undergo a rapid taper of these medications over a 24- to 48-hour period. Many such children will not subsequently exhibit drug dependency.
3. Signs and symptoms of withdrawal will develop within 24 hours of discontinuation or during the course of a rapid taper of an opioid. If this occurs, 1 of the rescue approaches in Table 4 can be chosen as a guide to facilitate conversion to enteral methadone management and to initiate a weaning strategy, with 2 caveats. Infants on very high daily doses of continuous intravenous opioid may require less than the

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TABLE 4 Weaning Protocols by Using Conversion of Continuous Opioid Infusions to Enteral Methadone and for Conversion of Midazolam (Versed) Infusion to Enteral Lorazepam (Ativan)

Robertson et al[149]
Conversion of continuous intravenous fentanyl of 7–14 d duration to enteral methadone: 1. By using the current hourly infusion rate, calculate the 24-h fentanyl dose. 2. Multiply the daily fentanyl dose by a factor of 100 to calculate the equipotent amount of methadone (ratio of potencies assumed to be fentanyl: methadone = 100:1). 3. Divide this amount of methadone by 6 (a correction for the longer half-life of methadone) to calculate an initial total daily dose of methadone, and on day 1 provide this amount orally in 4 divided doses every 6 h for 24 h. 4. Day 2: Provide 80% of original daily dose in 3 divided oral doses every 8 h for 24 h. 5. Day 3: Provide 60% of original daily dose in 3 divided oral doses every 8 h for 24 h. 6. Day 4: Provide 40% of original daily dose in 2 divided oral doses every 12 h for 24 h. 7. Day 5: Provide 20% of original daily dose × 1. 8. Day 6: Discontinue methadone. Conversion of continuous intravenous fentanyl greater than 14 d duration to enteral methadone: 1. Repeat steps 1–2 above. 2. Days 1–2: Divide the dose of methadone by 6 (a correction for the longer half-life of methadone) and on day 1 provide this amount orally in 4 divided doses every 6 h for 48 h. 3. Days 3–4: Provide 80% of original daily dose in 3 divided oral doses every 8 h for 48 h. 4. Days 5–6: Provide 60% of original daily dose in 3 divided oral doses every 8 h for 48 h. 5. Days 7–8: Provide 40% of original daily dose in 2 divided oral doses every 12 h for 48 h. 6. Days 9–10: Provide 20% of original daily dose once per day for 48 h. 7. Day 11: Discontinue methadone. For patients on continuous intravenous morphine, proceed as above but do not multiply the daily fentanyl dose by 100, because morphine and methadone are nearly equipotent.
Meyer and Berens[150]
Conversion of continuous intravenous fentanyl to intermittent intravenous morphine: 1. By using the target hourly infusion rate of fentanyl, calculate the 24-h fentanyl dose. 2. Multiply the daily fentanyl dose by a factor of 60 to calculate the equipotent dose of morphine (ratio of potencies assumed to be fentanyl: morphine = 60:1). 3. Divide the dose of morphine by 4 (correcting for the longer half-life of morphine) and on day 1 administer this amount intravenously in 6 divided doses every 4 h. 4. Titrate the morphine dose for adequate effect over 12 to 24 h. Conversion of intermittent intravenous morphine to enteral methadone: 1. Multiply the dose of morphine given every 4 h by 2 (ratio of potencies assumed to be morphine: methadone = 2:1) to determine an equipotent amount of methadone. 2. Provide this amount of methadone as an oral dose every 12 h for 3 doses. 3. Double this amount of methadone and provide as a single oral dose per day at bedtime. 4. Provide 90% of the initial dose on day 2, 80% on day 3, etc, so that the last dose of methadone (10% of the original dose) is given on day 10.
Protocols at Wolfson Children's Hospital, Jacksonville, Florida
Conversion of continuous intravenous fentanyl >7 d duration to enteral methadone: 1. By using the current hourly infusion rate, calculate the 24-h fentanyl dose. 2. Multiply the daily fentanyl dose by a factor of 100 to calculate the equipotent amount of methadone (ratio of potencies assumed to be fentanyl: methadone = 100:1). 3. Divide this amount of methadone by 8–12 (a correction for the longer half-life of methadone) to calculate an initial total daily dose of methadone (not to exceed 40 mg/day). 4. Days 1–2: Provide the total daily dose of methadone orally in 4 divided doses every 6 h for 48 h. At the time of the second methadone dose, reduce the fentanyl infusion rate to 50%; at the time of the third dose, reduce the fentanyl infusion rate to 25%; and after the fourth methadone dose, discontinue the fentanyl infusion. 5. Days 3–4: Provide 80% of original daily dose in 3 divided oral doses every 8 h for 48 h. 6. Days 5–6: Provide 60% of original daily dose in 3 divided oral doses every 8 h for 48 h. 7. Days 7–8: Provide 40% of original daily dose in 2 divided oral doses every 12 h for 48 h. 8. Days 9–10: Provide 20% of original daily dose once per day for 48 h. 9. Day 11: Discontinue methadone. Conversion of continuous intravenous midazolam >7 d duration to enteral lorazepam: 1. By using the current hourly infusion rate, calculate the 24-h midazolam dose. 2. Because lorazepam is twice as potent as midazolam and has a sixfold longer half-life, divide the 24 h midazolam dose by 12 to determine the daily lorazepam dose. 3. Divide the calculated lorazepam dose by 4 and initiate every 6 h oral treatments with the intravenous product or an aliquot of a crushed tablet. 4. Wean lorazepam by 10% to 20% per day. The dosage interval can also be increased gradually to every 8 h, then every 12 h, then every 24 h, and then every other day before lorazepam is discontinued.

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TABLE 4 Continued

Robertson et al[149]
Summary of Conversion Of Intravenous Opioids to Enteral Methadone
1. Tobias et al[147]: Converted 2 patients on morphine (0.1–0.15 mg/kg q3h) and 1 patient on fentanyl (1–2 μg/kg every 1–2 h) to methadone at a starting dose of 0.2 mg/kg per day. 2. Robertson et al[149]: 1 μg/kg per h fentanyl = 0.4 mg/kg per day methadone. 3. Meyer and Berens[150]: 1 μg/kg per h fentanyl = 0.24 mg/kg per day methadone. 4. Wolfson Children's Hospital: 1 μg/kg per h fentanyl = 0.2–0.3 mg/kg per day methadone.

calculated methadone equivalent to achieve a successful conversion. Also, the rate of weaning should be adjusted on the basis of careful continuing clinical assessment. Eighty percent of children can be successfully weaned from methadone completely within 5 to 10 days.

4. Signs and symptoms of withdrawal from benzodiazepine therapy can be delayed. Intravenous benzodiazepines can be converted to oral lorazepam (Table 4). The required time for weaning can be expected to be proportional to the duration of intravenous benzodiazepine treatment.
5. Infants and children at risk for withdrawal are prudently observed in the hospital for signs and symptoms. Each clinical unit can choose 1 assessment tool and train staff to minimize individual variability in scoring.
6. Discharge from the hospital for infants and very young children is prudently delayed until they are free of withdrawal signs and symptoms for a period of 24 to 48 hours after complete cessation of opioids. Earlier discharge of an older child can be individualized in consideration of the child's overall clinical status, the home environment, and the availability of adequate and prompt follow-up.
7. No clinical studies to date support the premise that initiation of clonidine, chloral hydrate, or continuous intravenous low-dose naloxone[157,158] during the course of continuous opioid infusions will reduce the likelihood or severity of opioid dependency.

CLINICAL HIGHLIGHTS

1) Each nursery that cares for infants with neonatal withdrawal should develop a protocol that defines indications and procedures for screening for maternal substance abuse. In addition, each nursery should develop and adhere to a standardized plan for the evaluation and comprehensive treatment of infants at risk for or showing signs of withdrawal.
2) Screening for maternal substance abuse is best accomplished by using multiple methods, including maternal history, maternal urine testing, and testing of newborn urine and/or meconium specimens that are in compliance with local laws. The screening of biological samples is an adjunct to provide additional information helpful in the ongoing medical care of the infant. The duration of urinary excretion of most drugs is relatively short, and maternal or neonatal urinary screening only addresses drug exposure in the hours immediately before urine collection. Thus, false-negative urine results may occur in the presence of significant intrauterine drug exposure. Although newborn meconium screening also may yield false-negative results, the likelihood is lower than with urinary screening. The more recent availability of testing of umbilical cord samples may be considered a viable screening tool, because it appears to reflect in utero exposures comparable to meconium screening.
3) Drug withdrawal should be considered in the differential diagnosis for infants in whom compatible signs develop. Physicians should be aware of other potential diagnoses that need to be evaluated and, if confirmed, treated appropriately.
4) Nonpharmacologic supportive measures that include minimizing environmental stimuli, promoting adequate rest and sleep, and providing sufficient caloric intake to establish weight gain should constitute the initial approach to therapy.
5) Signs of drug withdrawal can be scored by using a published abstinence assessment tool. Infants with confirmed drug exposure who are unaffected or demonstrating minimal signs of withdrawal do not require pharmacologic therapy. Caution should be exercised before instituting pharmacologic therapy that could lengthen the duration of hospitalization and interfere with maternal-infant bonding.

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Together with individualized clinical assessment, the serial and accurate use of a withdrawal assessment tool may facilitate a decision about the institution of pharmacologic therapy and thereafter can provide a quantitative measurement that can be used to adjust drug dosing.

6) The optimal threshold score for the institution of pharmacologic therapy by using any of the published abstinence assessment instruments is unknown.

7) Breastfeeding and the provision of expressed human milk should be encouraged if not contraindicated for other reasons.[111,159]

8) Pharmacologic therapy for withdrawal-associated seizures is indicated. Other causes of neonatal seizures must also be evaluated.

9) Vomiting, diarrhea, or both associated with dehydration and poor weight gain in the absence of other diagnoses are relative indications for treatment, even in the absence of high total withdrawal scores.

10) The limited available evidence from controlled trials of neonatal opioid withdrawal supports the use of oral morphine solution and methadone when pharmacologic treatment is indicated. Growing evidence suggests that oral clonidine is also effective either as a primary or adjunctive therapy, but further prospective trials are warranted. Dosing regimens are listed in Table 5. With respect to other drug treatments and clinical situations, a number of important caveats apply. Treatment with paregoric is contraindicated, because this preparation contains multiple opiates in addition to morphine, as well as other potentially harmful compounds (alcohol, anise). Morphine prescriptions should be written as milligrams of morphine per kilogram and not as milliliters of DTO per kilogram. Tincture of opium contains a 25-fold higher concentration of morphine than do available oral morphine solutions; hence, it increases the likelihood of drug error and morphine overdose. The relative efficacy and safety of buprenorphine for the treatment of NAS require additional comparative study. The optimal pharmacologic treatment of infants who are withdrawing from sedatives or hypnotics is unknown. Finally, there is also insufficient evidence to state whether an infant born to a mother with multiple drug abuse who meets criteria for pharmacologic therapy of withdrawal signs is best treated with an opioid, a barbiturate, a medication from another drug class, or a combination of drugs from different classes.

11) Physicians need to be aware that the severity of withdrawal signs, including seizures, has not been proven to be associated with differences in long-term outcome after intrauterine drug exposure. Furthermore, treatment of drug withdrawal may not alter the long-term outcome.

12) Given the natural history of withdrawal, it is reasonable for neonates with known antenatal exposure to opioids and benzodiazepines to be observed in the hospital for 4 to 7 days. After discharge, outpatient follow-up should occur early and include reinforcement of the education of the caregiver about the risk of late withdrawal signs.

13) Neonates cared for in ICUs who have developed tolerance to opioids and benzodiazepines as a result of an extended duration of treatment can be converted to an equivalent regimen of oral methadone and lorazepam. Doses may be increased as necessary to achieve patient comfort. These medications can then be reduced by 10% to 20% of the initial dose every 1 to 2 days on the basis of clinical response and serial assessments by using a standardized neonatal abstinence instrument.

14) Significant gaps in knowledge concerning the optimal treatment strategy (including the criteria for instituting pharmacologic therapy, the drug of first choice, and the strategy for weaning) of infants with neonatal withdrawal should be addressed in well-designed randomized controlled studies that are adequately powered to assess short-term outcomes and to provide for long-term follow-up.

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TABLE 5 Drugs Used in the Treatment of Neonatal Narcotic Withdrawal

Drug	Initial Dose	Increment	Maximum Dose	Ref. No.
Oral morphine	0.04 mg/kg every 3–4 h	0.04 mg/kg per dose	0.2 mg/kg per dose	119,121,126,133
Oral methadone	0.05–0.1 mg/kg every 6 h	0.05 mg/kg per dose	To effect	127
Oral clonidine	0.5–1 μg/kg every 3–6 h	Not studied	1 μg/kg every 3 h	132–135

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ERRATA

Committee on Infectious Diseases. Recommended Childhood and Adolescent Immunization Schedule—United States, 2014. *Pediatrics* 2014;133(2):357–363

Several corrections have been made in the online version of the American Academy of Pediatrics' "Recommended Childhood and Adolescent Immunization Schedule—United States, 2014" (*Pediatrics* 2014;133[2]:357–363; doi: 10.1542/peds.2013-3965). Please note that the following corrections have been made to the electronic version available at http://pediatrics.aappublications.org/content/133/2/357.full?sid=a26ca8bf-796e-47a4-82e8-35775f90c3a5 and that these corrections should be made to the version that appeared in the printed journal.

- In Fig 1 (0–18 yrs schedule), in the first box for Tetanus, diphtheria, & acellular pertussis, the parentheses should read: **(Tdap ≥7 yrs)**
- In Fig 1 (0–18 yrs schedule), in the first box for Meningococcal, the parentheses should read: **(Hib-MenCY: ≥6 weeks; MenACWY: ≥9 mos; MenACWY-CRM ≥2 mos)**
- Under Fig 1 (0–18 yrs schedule), the first URL should be **http://www.cdc.gov/vaccines/hcp/acip-recs/index.html**
- In Fig 2 (catch-up schedule), under Persons aged 4 months to 6 years, the entry for Inactivated poliovirus, Dose 2 to dose 3, should include footnote 7, so it should read: **4 weeks[7]**
- In Fig 2 (catch-up schedule), under Persons aged 7 through 18 years, the entry for Meningococcal, Dose 1 to dose 2, the parenthetical phrase should be deleted, so it should read: **8 weeks[13]**

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Hudak ML, Tan RC, The Committee on Drugs and the Committee on Fetus and Newborn. Neonatal Drug Withdrawal. *Pediatrics*. 2012;129;e540.

An error occurred in the Guidance for the Clinician by Hudak ML et al, titled "Neonatal Drug Withdrawal," published in the February 2012 issue of *Pediatrics* (2012;129(2):e540– e560; originally published online January 30, 2012; doi:10.1542/2012-3212). On page e547, the formatting of Fig 1 (Modified Finnegan's Neonatal Abstinence Scoring Tool) could be misinterpreted to indicate that 19 rather than 21 independent signs should be scored to assess the clinical severity of neonatal abstinence syndrome. The formatting has been changed (see Table) to differentiate clearly the 21 independent signs.

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NEONATAL ABSTINENCE SCORING SYSTEM

SYSTEM	SIGNS AND SYMPTOMS	SCORE	AM						PM					COMMENTS
CENTRAL NERVOUS SYSTEM DISTURBANCES (9 domains)	Continuous High Pitched (or other) Cry	2												
	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												
	Moderate-Severe Tremors Undisturbed	4												
	Increased Muscle Tone	2												
	Excoriation (Specific Area)	1												
	Myoclonic Jerks	3												
	Generalized Convulsions	5												
METABOLIC/VASOMOTOR/RESPIRATORY DISTURBANCES (8 domains)	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												
	Mottling	1												
	Nasal Stuffiness	1												
	Sneezing (>3-4 times/interval)	1												
	Nasal Flaring	2												
	Respiratory Rate >60/min	1												
	Respiratory Rate > 60/min with Retractions	2												
GASTROINTESTIONAL DISTURBANCES (4 domains)	Excessive Sucking	1												
	Poor Feeding	2												
	Regurgitation	2												
	Projectile Vomiting	3												
	Loose Stools	2												
	Watery Stools	3												
TOTAL SCORE														
INITIALS OF SCORER														

Adapted from: Nelson, Nicholas. Current Therapy in Neonatal-Perinatal Medicine. 2nd ed. Toronto: BC Decker, 1990[101]

Hwang et al. Discharge Timing, Outpatient Follow-up, and Home Care of Late-Preterm and Early-Term Infants," *Pediatrics.* 2013;132(1):101–108

An error occurred in the article by Hwang et al, "Discharge Timing, Outpatient Follow-up, and Home Care of Late-Preterm and Early-Term Infants," published in the July 2013 issue of *Pediatrics* (2013;132[1]:101–108; doi:10.1542/peds.2012-3892). On page 101, in the Abstract, on line 3 of the Results section, this reads: "(odds ratio [OR; 95% confidence interval (CI)]: 0.65 [0.54–0.79]; 0.95 [0.88–1.02])." This should have read: "(risk ratio [RR; 95% confidence interval (CI)]: 0.65 [0.54–0.79]; 0.95 [0.88–1.02])."

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An erratum has been published regarding this article. Please see the attached page for:
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