

# AMERICAN ACADEMY OF PEDIATRICS

Committee on Drugs

## Neonatal Drug Withdrawal

**ABSTRACT.** Maternal drug use during pregnancy may result in neonatal withdrawal. This statement presents current information about the clinical presentation, differential diagnosis, therapeutic options, and outcome for the offspring associated with intrauterine drug exposure.

ABBREVIATION. CNS, central nervous system.

### INCIDENCE

Intrauterine exposure to drugs may lead to neonatal intoxication or withdrawal. Multiple substances may be abused by women of childbearing age (Table 1). The incidence of drug-exposed newborns has been reported to be from 3% to 50%, depending on the specific patient population, with urban centers tending to report higher rates.<sup>1</sup> Although the number of drug-affected newborns increased by >300% between the years 1979 and 1987,<sup>2</sup> drug use among women of childbearing age has been reported to be slowly declining from an estimated 15% in 1985 to 8% in 1990.<sup>1,3</sup> Even with declining exposure rates, the problem of neonatal drug exposure is unlikely to disappear in the near future. Of the 4.1 million drug-abusing women of child-bearing age estimated from the 1995 and 1996 National Household Survey on Drug Abuse, ~3% are believed to continue drug use during pregnancy.<sup>4</sup>

Some compounds used during pregnancy have been demonstrated to cause withdrawal (Table 2). Among offspring exposed to opioids or heroin in utero, withdrawal signs will develop in 55% to 94%.<sup>5-8</sup> In contrast to the well-recognized neonatal opiate withdrawal syndrome, an abstinence syndrome after intrauterine cocaine exposure has not been clearly defined. Rather, it seems that abnormalities in infants exposed to cocaine reflect continued drug effects. In adults, withdrawal from cocaine is marked by drug craving, irritability, anorexia, and disturbed sleep and, until recently, was treated only with psychotherapy. Recent observations have suggested that cocaine withdrawal may be mediated by dopamine, serotonin, or both. Thus, dopamine agonists such as amantadine, desipramine, and bromocriptine; and serotonin antagonists such as tryptophan have been used in adults undergoing cocaine withdrawal.<sup>9</sup> No studies have been published that substantiate or quantify cocaine withdrawal in neonates.

The recommendations in this statement do 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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Many studies that assess behavior and neurologic signs in cocaine-exposed infants have used scoring systems designed to assess opiate withdrawal. Some of the signs of opiate abstinence are commonly scored (Tables 3 and 4), but these signs are toxic effects of cocaine rather than evidence of withdrawal. Cocaine or its metabolites have been found in neonatal urine for as long as 7 days after delivery.<sup>10</sup> Neurobehavioral abnormalities frequently occur in neonates with intrauterine cocaine exposure, most frequently on days 2 and 3; however, this is consistent with cocaine effect rather than with withdrawal.<sup>10</sup> Stimulant-exposed neonates (amphetamines, cocaine, or both) have been shown to be less symptomatic than opiate-exposed infants,<sup>11,12</sup> and infants exposed to stimulants and narcotics had abstinence scores similar to those for infants exposed only to opioids.<sup>13</sup> In an unblinded study, all drug-exposed infants, including those exposed only to cocaine, had more severe abstinence signs on an opiate scoring system than the unexposed group. Of the infants, 6%, 14%, and 35% of infants exposed to cocaine only, heroin only, or cocaine plus heroin, respectively, qualified for treatment based on scoring.<sup>14</sup> In the only study in which observers blinded to infant drug exposure performed the observations, no differences in withdrawal signs were seen between cocaine-exposed and unexposed infants.<sup>15</sup> Finnegan et al<sup>16</sup> have suggested a separate scoring instrument might be appropriate to assess cocaine exposure.

### CLINICAL PRESENTATION

The clinical presentation of neonatal drug withdrawal is variable, depending on the drug(s), timing and amount of the last maternal use, maternal and infant metabolism and excretion, and other unidentifiable factors. Generally, the signs of opiate withdrawal (Table 3) include evidence of central nervous system (CNS) irritability and gastrointestinal dysfunction. The CNS irritability is accompanied by seizures in 2% to 11% of infants withdrawing from opioids,<sup>17-19</sup> however, abnormal electroencephalograms without overt seizure activity have been reported in >30%.<sup>20,21</sup> Seizures also may be associated with nonnarcotic (barbiturates,<sup>22,23</sup> alcohol,<sup>24</sup> sedative-hypnotics<sup>25</sup>) withdrawal. The mechanism and significance of withdrawal-associated seizures are unclear.

The timing of withdrawal onset depends on the time of the last drug exposure and the metabolism and excretion of the drug and its metabolites. If  $\geq 1$  week has elapsed between the last maternal use and delivery, the incidence of neonatal withdrawal is

**TABLE 1.** Major Drugs of Abuse<sup>a</sup>

Opioids	CNS Stimulants	CNS Depressants	Hallucinogens
Agonists	Amphetamines	Alcohol	Indolealkylamines (LSD,
Morphine	Dextroamphetamine	Barbiturates	psilocybin, psilocybin, DMT,
Codeine	[Desozyn]	Benzodiazepines	DET)
Methadone	Methamphetamine [Desozyn]	Other sedative-hypnotics	Phenylethylamines
Meperidine [Demerol]	Amphetamine sulfate	Methaqualone [Quaalude]	(mescaline, peyote)
Oxycodone [Percodan]	Amphetamine congeners	Ethchlorvynol [Placidyl]	Phenylisopropylamines
Propoxyphene [Darvon]	Benzphetamine [Didrex]	Glutethimide [Doriden]	(MDA, MMDA, MDMA,
Hydromorphone [Dilaudid]	Diethylpropion [Tenuate, Tepanil]	Methypylon [Noludar]	MDEA)
Fentanyl [Sublimaze]	Fenfluramine [Pondimin]	Ethinamate [Valmid]	Inhalants
Heroin	Mazindol [Mazanor, Sanorex]	Chloral hydrate	Solvents and aerosols (glues,
Antagonists	Phendimetrazine [Adipost,	Cannabinoids	gasoline, paint thinner,
Naloxone [Narcan]	Bontril, Prelu-2]	Marijuana	cleaning solutions, nail
Naltrexone [Trexan]	Phenmetrazine [Preludin]	Hashish	polish remover, freon)
Mixed Agonist-antagonists	Phentermine [Fastin, Obermine,		Nitrites
Pentazocine [Talwin]	Phentrol]		Nitrous oxide
Nalbuphine [Nubain]	Cocaine		
Buprenorphine	Methylphenidate (Ritalin)		
[Buprenex]	Pemoline (Cylert)		
Butorphanol [Stadol]	Phenylpropanolamine		
	Phencyclidines		

<sup>a</sup> Adapted from Milhorn HT. Pharmacologic management of acute abstinence syndromes. *Am Fam Physician.* 1992;45:231  
 LSD indicates lysergic acid diethylamide; DMT, dimethyltryptamine; DET, diethyltryptamine; MDA, methylenedioxyamphetamine; MMDA, 3-methoxy-4,5-methylenedioxyamphetamine; MDMA, 3,4-methylenedioxymethamphetamine; and MDEA, 3,4-methylenedioxyethamphetamine.

relatively low.<sup>26</sup> The longer the half-life of elimination, the later withdrawal tends to occur. Withdrawal from ethanol begins early, generally during the first 3 to 12 hours after delivery.<sup>24,27</sup> The onset of narcotic withdrawal, including methadone withdrawal, is frequently during the first 48 to 72 hours,<sup>18</sup> but may be delayed as late as 4 weeks.<sup>19</sup> Diagnosis of sedative-hypnotic withdrawal is more difficult because classically it appears after the first few days after birth. Barbiturate withdrawal has a median onset of 4 to 7 days, but a wide range from days 1 through 14.<sup>22,28</sup> Other sedative-hypnotics have exhibited even later onset, including as late as day 12 for diazepam<sup>29</sup> and day 21 for chlordiazepoxide.<sup>30</sup> Subacute signs of narcotic drug withdrawal may last up to 6 months.<sup>31</sup> Most studies demonstrate that larger maternal methadone dosages in late pregnancy are associated

with greater neonatal concentrations and increased risk for withdrawal.<sup>32-35</sup> Larger maternal dosages were associated with faster declines in neonatal concentrations and more severe CNS withdrawal in 21 infants born to methadone-dependent women.<sup>34</sup> In the only study failing to note a correlation between neonatal serum levels and maternal methadone dose at delivery or maternal serum levels, the mothers also abused other drugs, and a radioimmunoassay that exhibited 50% cross-reactivity with one methadone metabolite was used to determine methadone concentrations.<sup>36</sup> Currently, many obstetricians reduce the mother's daily methadone dosage to ≤20 mg/kg because several studies have demonstrated a lower incidence and decreased severity of neonatal withdrawal with lower dosages.<sup>7,8,37</sup> Others are reluctant to wean maternal methadone in late pregnancy

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

Drug	Signs	Duration of Signs*	Reference
Alcohol	Hyperactivity, crying, irritability, poor suck, tremors, seizures, onset of signs at birth, poor sleeping pattern, hyperphagia, diaphoresis	18 mo	24,27
Barbiturates	Irritability, severe tremors, hyperacusis, excessive crying, vasomotor instability, diarrhea, restlessness, increased tone, hyperphagia, vomiting, disturbed sleep; onset first 24 hours of life or as late as 10 to 14 days of age	4-6 mo with Rx	22,28
Caffeine	Jitteriness, vomiting, bradycardia, tachypnea	1-7 d	102
Chlordiazepoxide	Irritability, tremors; signs may start at 21 days	9 mo; 1½ mo with Rx	30
Clomipramine	Hypothermia, cyanosis, tremors; onset 12 hours of age	4 d with Rx	103
Diazepam	Hypotonia, poor suck, hypothermia, apnea, hypertonia, hyperreflexia, tremors, vomiting, hyperactivity, tachypnea (mother receiving multiple drug therapy)	8 mo; 10-66 d with Rx	29,104
Ethchlorvynol	Lethargy, jitteriness, hyperphagia, irritability, poor suck, hypotonia (mother receiving multiple drug therapy)	Possibly 10 d with Rx	105
Glutethimide	Increased tone, tremors, opisthotonos, high-pitched cry, hyperactivity, irritability, colic	6 mo	106
Hydroxyzine	Tremors, irritability, hyperactivity, jitteriness, shrill cry, myoclonic jerks, hypotonia, increased respiratory and heart rates, feeding problems, clonic movements (mother receiving multiple therapy)	5 wk with Rx	25
Meprobamate	Irritability, tremors, poor sleep patterns, abdominal pain	9 mo; 3 mo with Rx	107

\* Rx indicates the infant was treated with pharmacologic agents, and the natural course of the signs may have been shortened.

**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 weight gain
Exaggerated Moro reflex	Autonomic Signs
Seizures	Increased sweating
Frequent yawning and sneezing	Nasal stuffiness
	Fever
	Mottling
	Temperature instability

out of concern that the mother may turn to other illicit drugs.<sup>38</sup> In fact, some authors suggest increasing maternal methadone late in pregnancy based on lower maternal methadone plasma levels for the same dose.<sup>38,39</sup>

**POLYDRUG USE**

Polydrug use may occur with multiple combinations of various drugs. Of these possibilities, the simultaneous use of opioids and cocaine has been commonly reported. Cocaine enhances the analgesic effect of morphine<sup>40</sup> and blocks the tolerance that develops to morphine analgesia.<sup>41</sup> In rats, short-term cocaine exposure decreased the severity of naloxone-induced opiate withdrawal.<sup>42</sup> Two studies in humans have demonstrated that naloxone-induced withdrawal in adults abusing both cocaine and opioids was less severe than that of addicts abusing only opioids.<sup>42,43</sup> The mechanism of this interaction may be cocaine-induced reduction in  $\alpha_2$ -adrenergic activity in the locus ceruleus neurons.<sup>44</sup>

The effect of polydrug use on the occurrence and severity of neonatal abstinence is controversial. Abstinence scores of 61 infants whose mothers abused both cocaine and methadone were similar to the scores of 42 infants whose mothers received high-dose maintenance methadone.<sup>33</sup> Similarly, use of

multiple opiates did not alter the severity of withdrawal. The neurobehavioral scores of 12 infants exposed to intrauterine cocaine were similar to the scores of 11 infants exposed to both cocaine and methadone, except for the consolability score, for which infants exposed to both drugs scored better.<sup>45</sup> Higher abstinence scores have been reported in infants exposed to both cocaine and heroin ( $n = 17$ ) compared with heroin ( $n = 14$ ) or cocaine ( $n = 35$ ) alone, resulting in treatment of 35%, 14%, and 6%, respectively.<sup>14</sup>

**DIFFERENTIAL DIAGNOSIS**

A physician who is unaware of a mother's drug ingestion may mistake the signs of withdrawal for other common neonatal problems, such as colic or infection. If the signs in the infant are consistent with drug withdrawal, specimens of neonatal urine or meconium should be obtained for testing. Differentiating neonatal signs of drug withdrawal from irritability of the CNS resulting from infectious or metabolic disorders, such as hypoglycemia and hypocalcemia, may be difficult; no clinical signs should be attributed solely to drug withdrawal without appropriate assessment and diagnostic tests to rule out other causes. Thus, the identification of infants at risk for withdrawal is important. A detailed maternal drug history should be obtained, including prescription and nonprescription drugs received, social habits of the parents, and whether the mother is breastfeeding. Maternal self-reporting frequently underestimates drug exposure, and maternal urine screening during pregnancy fails to identify many cases of drug use.<sup>46</sup> Urine screening of the newborn will have a high false-negative rate because only results for infants with recent exposure will be positive. Meconium drug testing, although not conclusive if results are negative, is more likely to identify infants of drug-abusing mothers than is infant urine testing.<sup>47,48</sup>

Before the onset of withdrawal signs, the presence of maternal or infant characteristics known to be associated with drug use in pregnancy can be con-

**TABLE 4.** Neonatal Drug-Withdrawal Scoring System

Signs	Score			
	0	1	2	3
Tremors (muscle activity of limbs)	Normal	Minimally increased when hungry or disturbed	Moderate or marked increase when undisturbed; subside when fed or held snugly	Marked increase or continuous even when undisturbed, going on to seizure-like movements
Irritability (excessive crying)	None	Slightly increased	Moderate to severe when disturbed or hungry	Marked even when undisturbed
Reflexes	Normal	Increased	Markedly increased	
Stools	Normal	Explosive, but normal frequency	Explosive, more than 8 d	
Muscle tone	Normal	Increased	Rigidity	
Skin abrasions	No	Redness of knees and elbows	Breaking of the skin	
Respiratory rate/minute	<55	55-75	76-95	
Repetitive sneezing	No	Yes		
Repetitive yawning	No	Yes		
Vomiting	No	Yes		
Fever	No	Yes		

Reprinted with permission from Lipsitz PJ. *Clin Pediatr.* 1975;14:592-594.

sidered indications to screen for intrauterine drug exposure, by using meconium or urine samples. Maternal characteristics that suggest a need for screening include no prenatal care, previous unexplained fetal demise, precipitous labor, abruptio placentae, hypertensive episodes, severe mood swings, cerebrovascular accidents, myocardial infarction, and repeated spontaneous abortions.<sup>45,46,49–53</sup> Infant characteristics that may be associated with maternal drug use include prematurity,<sup>11,52</sup> unexplained intrauterine growth retardation,<sup>50,52</sup> neurobehavioral abnormalities,<sup>54</sup> urogenital anomalies,<sup>55</sup> and atypical vascular incidents, such as cerebrovascular accidents,<sup>10</sup> myocardial infarction,<sup>56</sup> and necrotizing enterocolitis in otherwise healthy full-term infants.<sup>52</sup> The legal implications of testing and the need for consent from the mother may vary among the states;<sup>57</sup> therefore, pediatricians should be aware of local laws and legislative changes that may influence regional practice.

Preterm infants have been described as being at lower risk for drug withdrawal. Infants <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.<sup>33</sup> The apparent decreased severity of abstinence in preterm infants may relate to developmental immaturity of the CNS or to differences in total drug exposure. Alternatively, the evaluation of the severity of abstinence signs may be more difficult in preterm infants, because scoring tools to describe withdrawal were largely developed in term or near-term infants.<sup>58,59</sup> Preterm infants are likely to score relatively higher for tremors, high-pitched cry, tachypnea, and poor feeding, but lower for sleep pattern, tone, fever, stool pattern, and reflexes. Thus, an instrument to quantify abstinence in preterm infants is needed. Given the current absence of a scoring instrument for preterm infants, health care professionals may consider treatment if the infant is too ill to assess possible withdrawal or is not thriving as expected.

#### SUPPORTIVE TREATMENT

Initial treatment of the neonate experiencing drug withdrawal should be primarily supportive, because pharmacologic therapy may prolong hospitalization and subject the infant to exposure to drugs that may not be indicated. Supportive care includes swaddling to decrease sensory stimulation; frequent small feedings of hypercaloric (24 cal/oz) formula to supply the additional caloric requirements; and observation of sleeping habits, temperature stability, weight gain or loss, or change in clinical status that might suggest another disease process. Supportive care in the form of intravenous fluids and replacement electrolytes may be necessary to stabilize the infant's condition in the acute phase without the need for pharmacologic intervention. The clinical signs of many infants who manifest drug withdrawal may be treated in this manner. Additional assessment of infants of drug-abusing mothers includes screening for hepatitis B and C and sexually transmitted diseases, including human immunodeficiency virus infection.<sup>46</sup>

Excess weight loss may represent inadequate pro-

vision of calories rather than the need for pharmacologic therapy. In addition to the caloric expenditure caused by increased activity, crying, and decreased sleep, calories may be lost through vomiting, drooling, and diarrhea. Caloric intake should be calculated daily to provide the 150 to 250 cal/kg per day necessary for proper growth in neonates suffering with withdrawal.<sup>60,61</sup>

#### PHARMACOLOGIC THERAPY

The decision to use drug therapy must be individualized, based on the severity of withdrawal signs and an assessment of the risks and benefits of therapy. Withdrawal from sedative-hypnotic drugs or narcotics may be life-threatening. However, drug withdrawal is a self-limited process. The known benefit of pharmacologic treatment is short-term amelioration of clinical signs; whether long-term morbidity related to neonatal drug withdrawal is decreased by pharmacologic management of symptomatic infants remains unproven. The risk of compounding intrauterine induced deficits with neonatal exposure to other drugs is unknown. Furthermore, some authors believe that pharmacologic therapy of the infant may reinforce the maternal idea that discomfort or annoying behavior should be treated with drugs.<sup>62</sup>

Infants with confirmed drug exposure who do not have signs of withdrawal do not require therapy. Indications for drug therapy are seizures, poor feeding, diarrhea, and vomiting resulting in excessive weight loss and dehydration, inability to sleep, and fever unrelated to infection. It is essential that infection, hypoglycemia, hypocalcemia, hypomagnesemia, hyperthyroidism, CNS hemorrhage, and anoxia be ruled out as the cause of the signs. Each nursery should adopt an abstinence scoring method to measure the severity of withdrawal.<sup>8,57,58,63–67</sup> The Lipsitz tool<sup>57</sup> (Table 4) offers the advantages of a relatively simple numeric system and a reported 77% sensitivity using a value >4 as an indication of significant withdrawal signs. Other well-recognized methods include those developed by Finnegan<sup>63</sup> and Ostrea.<sup>64</sup> The Finnegan method using a weighted scoring of 31 items may be too complex for routine use in a busy clinical service. The 6 criteria in the Ostrea system are feasible, but the method is limited by the use of simple ranking rather than a numeric scale, precluding summing the severity scores of multiple signs of withdrawal. Regardless of the system chosen, use of an abstinence scoring sheet results in more objective criteria for determining when pharmacologic treatment is necessary and whether a drug dose should be increased or decreased.

If pharmacologic management is chosen, relatively specific therapy, that is, a drug from the same class as that causing withdrawal, is preferable. The only drugs approved by the US Food and Drug Administration for the treatment of drug withdrawal are the benzodiazepines for alcohol withdrawal and methadone for opioid withdrawal. However, substantial favorable experience has been reported with several agents that are not approved by the US Food and Drug Administration, such as paregoric, tincture of

opium, morphine, clonidine, phenobarbital, chlorpromazine, and diazepam.

Improvement in abstinence scores should assist in assessing the appropriate timing for decreasing the dose of the drug chosen. Guides to adequate therapy include a normal temperature curve, the ability of the infant to sleep between feeding and medications, a decrease in activity and crying, a decrease in motor instability, and weight gain.

### COMPARATIVE STUDIES

Only a few studies compare the efficacy of different treatments of neonatal drug withdrawal. Data about the relationship between the severity of withdrawal, the short-term efficacy of treatment, or, importantly, the longer-term infant outcome after different treatment regimens are not reported. Sixty-nine infants of mothers maintained with methadone were assigned to one of the four following treatment regimens: paregoric, phenobarbital (titration), phenobarbital loading, and diazepam.<sup>68</sup> When treatment was not successful with the assigned agent, one of the other agents was used. Monotherapy with paregoric was successful in 21 (91%) of 23 infants, whereas phenobarbital was successful in 9 (45%) of 20 (loading) and 8 (50%) of 16 (titrated). Diazepam was never successful as a single agent. A set total abstinence score was required for enrollment; however, groups were not compared for severity of abstinence scores. No information was given about screening of the mothers or infants for other drugs, and drug dosages were not reported. Scores on the Bayley Infant Development scale were similar for all treatment groups, and all were within the normal range. In addition, they were similar to scores of infants who did not require treatment.

In an open, nonrandomized study, Pacifico and colleagues<sup>69</sup> suggested that morphine alone, in dosages ranging from 0.4 to 1 mg/kg/day orally, was superior to diazepam (3 to 6 mg/kg/day intravenously or orally) combined with phenobarbital (8 to 15 mg/kg/day intravenously or intramuscularly) and superior to the combination of morphine, diazepam, and phenobarbital. However, in addition to nonrandom assignment, the dosage of drugs varied without explanation, and baseline withdrawal severity may have been different among groups.<sup>69</sup>

In a randomized study of infants of drug-dependent mothers during the first 2 weeks after birth, infants treated with paregoric ( $n = 16$ ) did not differ from infants treated with phenobarbital ( $n = 15$ ) in weight gain or vital signs.<sup>70</sup> However, the paregoric-treated infants required a significantly longer treatment (22 days) compared with phenobarbital-treated infants (17 days). Although all infants had Finnegan scores  $>8$  to be treated, no information about comparability of severity of withdrawal before treatment was given. In addition, maternal groups received comparable doses of methadone, but some mothers in each group abused other drugs.

In a randomized study, Kandall and coworkers<sup>71</sup> found paregoric (0.2 mL/kg every 3 hours, increased as needed by 0.05 mL) superior to phenobarbital (5 mg/kg/day intramuscularly every 8 hours, in-

creased as needed by 1 mg/kg/day); withdrawal seizures developed in 7 of 62 infants treated with phenobarbital, compared with none of the 49 infants treated with paregoric. The course of severity of withdrawal in the two groups was similar. In this study, infants had similar withdrawal severity scores before treatment, and approximately half of the mothers in both groups abused multiple drugs.

### SPECIFIC AGENTS FOR OPIOID WITHDRAWAL

#### Tincture of Opium

If opiate treatment of withdrawal is used, tincture of opium (10 mg/mL) is preferred to paregoric. A 25-fold dilution of tincture of opium contains the same concentration of morphine equivalent as paregoric (0.4 mg/mL morphine equivalent) without the additives or high alcohol content found in paregoric. Because of the danger of mistaking tincture of opium for paregoric, tincture of opium is best dispensed to the nursery in a dilution that contains a concentration of morphine equivalent to the concentration in paregoric. Diluted tincture of opium should be administered according to the same morphine-equivalent dosage schedule used for paregoric. Thus, the recommended starting dose of the diluted solution is 0.1 mL/kg or 2 drops/kg with feedings every 4 hours. Dosing may be increased by 2 drops/kg every 4 hours as needed to control withdrawal signs. After withdrawal symptomatology has been stabilized for 3 to 5 days, the tincture of opium dosage may be tapered by a gradual decrease in the dose without altering the frequency of administration.

#### Paregoric

Paregoric, containing anhydrous morphine (0.4 mg/mL), was one of the first agents used for the treatment of opioid withdrawal in neonates. Infants treated with paregoric for narcotic withdrawal signs had a more physiologic sucking pattern, higher nutrient consumption, higher percentage of sucking time, greater sucking pressure exerted at nursing, and more weight gain than infants treated with diazepam or phenobarbital.<sup>72</sup> Seizures developed subsequently in only 2 of 48 infants initially treated for signs of withdrawal with paregoric, compared with 5 of 12 infants treated with diazepam.<sup>17</sup>

The initial dose of paregoric administered to a full-term infant for treatment of neonatal narcotic withdrawal is 0.1 mL/kg (2 drops/kg) with feedings every 4 hours. Dosing may be increased by 2 drops/kg every 3 to 4 hours until the signs of withdrawal are controlled. After withdrawal signs are controlled for 3 to 5 days, the dosage of paregoric should be tapered by gradually decreasing the dose, not by increasing the dosing interval.

The use of paregoric has declined because of the known and potential toxic effects of its many ingredients. In addition to morphine, it contains isoquinoline derivatives (noscapine and papaverine), which are antispasmodics. Paregoric contains several potentially toxic compounds. Camphor, a CNS stimulant, is eliminated from the body slowly because of its high lipid solubility and the need for glucuronic

conjugation for urinary excretion. Paregoric contains a high concentration of ethanol (44% to 46%), a CNS depressant, and anise oil, which may cause habituation. Benzoic acid (4 mg/mL), an oxidative product of benzyl alcohol, is present and may compete for bilirubin binding sites. In addition, the formation of benzoic acid from benzyl alcohol was mechanistically important in the production of severe acidosis, CNS depression, respiratory distress, hypotension, renal failure, seizures, and death reported in small premature infants who received benzyl alcohol in amounts of 99 to 234 mg/kg per 24 hours.<sup>73-75</sup> Glycerin is another component of paregoric; pulmonary edema was reported after the use of paregoric in a 3-week-old term infant with diarrhea.<sup>76</sup> An additional disadvantage of paregoric therapy is that longer duration of therapy (from 23 to 45 days) may be required.

### Morphine

In the past, parenteral morphine was used to treat the severe vasomotor collapse observed in infants with heroin withdrawal with or without associated seizures.<sup>59,77</sup> Physicians treating neonates should be aware that the parenteral formulation of morphine contains sodium bisulfite and phenol, both of which have been associated with adverse effects in newborns. However, the amount of additives in standard doses of morphine may not be large enough to affect the infant significantly. Sodium bisulfite has been reported to produce an anaphylactic reaction consisting of pruritus, flushing, and acute wheezing in older patients.<sup>78</sup> Percutaneous absorption of phenol has been associated with two cluster outbreaks of severe jaundice in small infants.<sup>79</sup> The dose of phenol that produces hyperbilirubinemia is unknown.

An oral preparation of morphine (2 and 4 mg/mL) that contains no additives and less alcohol (10%) than paregoric is now available. Oral morphine has less of an analgesic effect than the same parenteral dose. To date, there have been no reported studies in which a morphine preparation with morphine equivalent to paregoric has been used to treat neonatal narcotic withdrawal. Oral morphine doses should be calculated to deliver to the full-term infant the same quantity of morphine equivalent usually supplied in paregoric.

Safety of opiate preparations in neonates is a justified concern because of their marked respiratory depressant effect, even at therapeutic doses. Life-threatening reactions have been reported in nonnarcotic habituated infants younger than 3 months who were premedicated with morphine (0.1 mg/kg) for imaging studies.<sup>80</sup> However, adverse side effects in infants manifesting narcotic withdrawal may be more refractory to this dose.

### Methadone

The neonatal abstinence syndrome has been treated with methadone. Pharmacokinetic data have been published about neonates,<sup>35</sup> and methadone has been used to treat opioid withdrawal in a small number of children.<sup>81</sup> Initial doses of 0.05 to 0.1 mg/kg may be given every 6 hours,<sup>82</sup> with increases

of 0.05 mg/kg given until signs are controlled. After signs are controlled, methadone may be given every 12 to 24 hours and discontinued after weaning to doses of 0.05 mg/kg per day. After discontinuation, a continued slow fall in plasma concentration will occur because of the long half-life (26 hours) of methadone. The oral formulation of methadone contains 8% ethanol.

### Clonidine

Clonidine is a nonnarcotic medication that effectively reduces withdrawal signs in adults; its mechanism of action specifically targets the adrenergic hyperactivity postulated to be the basis of the narcotic withdrawal syndrome. At low doses, clonidine stimulates  $\alpha_2$  presynaptic adrenergic receptors, thereby decreasing the amount of norepinephrine released into the synapse and lowering the firing rate of adrenergic neurons. In an open trial, six of seven infants with neonatal narcotic withdrawal signs were treated effectively with oral clonidine (0.5 to 1.0  $\mu$ g/kg in a single dose, followed by a maintenance dose of 3 to 5  $\mu$ g/kg/day, divided every 4 to 6 hours).<sup>83</sup> Some infants had immediate reversal of withdrawal signs after a single dose of clonidine. Clonidine blood levels were 0.1 to 0.3 ng/mL. The infant who remained symptomatic while receiving clonidine was the infant of a mother who received, in addition to methadone, haloperidol, desipramine, and theophylline. The only sign that seemed refractory to clonidine therapy was poor sleeping. Mild metabolic acidosis, which resolved without therapy or change in clonidine administration, developed in two infants. Neither hypotension nor other adverse effect was noted. The length of therapy of infants treated with clonidine was significantly shorter than that of a retrospective sample treated with phenobarbital, 13 versus 27 days, respectively ( $P < .05$ ). Larger controlled trials and pharmacokinetic data are needed before clonidine can be advocated as routine treatment. An oral liquid form is not available commercially. Although benzodiazepines remain the choice of therapy for alcohol withdrawal in adults, clonidine has been shown to be superior to chlordiazepoxide in decreasing the anxiety, hypertension, and tachycardia of alcohol withdrawal.<sup>84</sup>

### Chlorpromazine

The CNS and gastrointestinal signs produced by narcotic withdrawal are controlled by chlorpromazine.<sup>65</sup> A dosage of 0.55 mg/kg every 6 hours intramuscularly or orally has been used in infants. Occasionally, hypothermia may develop. Chlorpromazine is eliminated very slowly in the neonate, with a reported half-life of 3 days.<sup>85</sup> Chlorpromazine contains sodium chloride (6 mg/mL), sodium bisulfite (1 mg/mL), and sodium sulfite (1 mg/mL). Some injectable formulations contain benzyl alcohol (2%); however, other formulations do not. The prolonged excretion time and multiple side effects of chlorpromazine, including cerebellar dysfunction, decreased seizure threshold, and hematologic problems, limit its usefulness in the neonate.

## Phenobarbital

Hyperactive behavior in the infant who manifests narcotic withdrawal is modified by administration of phenobarbital, but the drug does not relieve the gastrointestinal signs.<sup>86</sup> Large doses of phenobarbital may depress the CNS of the infant significantly, impair the suck reflex, and delay bonding between mother and infant.<sup>71</sup> Other disadvantages include a very long half-life, induction of drug metabolism, and rapid tolerance to the sedative effect. No comparative studies have shown an advantage of phenobarbital over chlorpromazine, diazepam, or methadone.<sup>7,65</sup>

The therapeutic blood level of phenobarbital necessary for control of narcotic withdrawal signs is unknown. A neonatal loading dosage of 16 mg/kg per 24 hours of phenobarbital that produced blood levels of 20 to 30 mg/mL controlled signs of narcotic withdrawal effectively.<sup>87</sup> The blood level should be measured 24 to 48 hours later, and the maintenance dose adjusted according to the infant's symptomatology, as determined by the abstinence score and the phenobarbital plasma level. Finnegan and coworkers<sup>87</sup> reported that maintenance doses of 2 to 8 mg/kg per 24 hours were required to control withdrawal symptomatology and maintain phenobarbital plasma levels. After the infant's condition has stabilized, the maintenance dose should be decreased to allow the drug concentration to decrease by 10% to 20% per day.

Although not a first-choice drug for narcotic withdrawal, phenobarbital may be one drug of choice for nonnarcotic-related withdrawal signs.

## Diazepam

Rapid suppression of narcotic withdrawal signs has been observed in infants treated with diazepam (1.0 to 2 mg every 8 hours).<sup>88</sup> However, the following multiple concerns exist about the use of diazepam<sup>89,90</sup>:

1. The newborn infant has a limited capacity to metabolize and excrete diazepam. The total elimination of diazepam and its metabolites may take  $\geq 1$  month.<sup>91</sup>
2. Poor sucking and increased sedation have been reported.<sup>59,68,72</sup>
3. Late-onset seizures have been observed in infants treated with diazepam.<sup>19</sup>
4. Parenteral diazepam contains benzyl alcohol (1.5%). However, the amount of benzyl alcohol administered during diazepam withdrawal therapy is not problematic. A 3-kg neonate would receive only 2 mg/kg per day of benzyl alcohol, about 50-fold less than that associated with toxic effects.<sup>73</sup>
5. Parenteral diazepam also contains sodium benzoate (5%) that displaces bilirubin from albumin. Some decrease in albumin binding capacity has been demonstrated in addicted infants treated with diazepam.<sup>84</sup> Thus, the use of diazepam is contraindicated in a jaundiced or premature infant.<sup>92</sup>

6. Parenteral diazepam contains ethanol (10%) and substantial quantities of propylene glycol (40%). Cerebral and hepatic dysfunction and hyperosmolality with an osmolar gap have been reported in infants receiving large quantities (10 mL/24 hours) of parenteral multivitamins, which contain 30% propylene glycol.<sup>93,94</sup>
7. In a comparative trial, diazepam was never successful as a single agent in treating withdrawal signs adequately in 10 children.<sup>68</sup>

Benzodiazepines other than diazepam, in particular, lorazepam and chlordiazepoxide, have been widely used in adults for alcohol withdrawal. Other benzodiazepines have not been studied adequately.

## NALOXONE USE IN NEONATES: POTENTIAL FOR SEVERE WITHDRAWAL

Concern about the use of naloxone has been raised after a reported case of apparent naloxone-induced seizures.<sup>95</sup> Seizures developed 2 minutes after a 0.2 mg intramuscular dose of naloxone in an apneic intubated infant of a mother who had taken 60 mg of methadone 8 hours before a cesarean section for fetal distress. The seizure did not respond to administration of diazepam, paraldehyde, or phenobarbital, but terminated with a bolus of morphine (0.1 mg/kg). After termination of a subsequent morphine infusion, other features of opioid withdrawal developed in the infant. Currently, it is stated that administration of naloxone to the infant of a narcotic-addicted mother may result in neonatal seizures because of abrupt drug withdrawal.<sup>96</sup> Hospitals used frequently by drug-dependent women may consider avoiding naloxone for fear of inadvertently precipitating neonatal withdrawal in infants delivered to previously unrecognized opioid abusers. Although the case reported is worrisome, data about the frequency of significant adverse outcomes after the use of naloxone in narcotic-habituated infants are unavailable. Naloxone-precipitated rapid withdrawal is used therapeutically in adults to speed the detoxification process. Within 5 minutes of injection of the antagonist, withdrawal signs appear, peak in 10 to 20 minutes, and subside in  $\sim 1$  hour.<sup>97</sup> Physicians in Germany have recommended a small dose of naloxone (0.01 mg/kg) as delivery room treatment of apnea in infants of mothers who abused opioids during pregnancy.<sup>98</sup> Data are inadequate to suggest removing naloxone as one of several therapeutic options for managing respiratory depression in the delivery room. However, physicians should be aware of the potential risk of rapid withdrawal and be prepared to treat withdrawal in the delivery room.

## OUTCOME

Long-term morbidity from neonatal drug withdrawal remains unstudied. Few studies have followed drug-exposed children beyond the first few years of life. Confounding variables, such as environment and dysfunctional caregivers, make determining the causes of outcome differences difficult. In a small study, developmental scores on the mental index on the Bayley Scales of Infant Development were not affected by se-

verity of withdrawal or the treatment chosen.<sup>68</sup> Mean scores on the Bayley Scales of Infant Development were ~103 for all infants treated for withdrawal, including those receiving phenobarbital ( $n = 17$ ), paregoric ( $n = 21$ ), or combination therapy ( $n = 31$ ).<sup>68</sup> Scores of infants whose withdrawal was too mild to qualify for therapy ( $n = 16$ ) also were similar.

Of 14 infants with withdrawal-associated seizures, the abstinence scores for 5 infants were  $<7$  (the cutoff for treatment), and they received no 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 those. Electroencephalograms were abnormal in 9 neonates; however, results of 7 of 8 of these became normal during follow-up. Mean scores on the Bayley Scales of Infant Development were normal by 1 year of age, similar to matched controls who were drug-exposed but in whom withdrawal-associated seizures did not develop.<sup>99</sup> Withdrawal-associated seizures seem to be primarily myoclonic, respond to opiates, and 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 neurotransmitters.<sup>100,101</sup> The normalization of the electroencephalogram and normal neurologic development are believed to reflect recovery of normal neurotransmitter concentrations during early infancy.

### RECOMMENDATIONS

1. Screening for maternal substance abuse should involve multiple forms, including maternal history, maternal urine testing, and testing of newborn urine and newborn meconium specimens. 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.
2. Drug withdrawal should be considered as a diagnosis in infants in whom compatible signs develop. Physicians should be aware of other potential diagnoses that should be evaluated and treated, if confirmed.
3. Drug withdrawal should be scored using an appropriate scoring tool. Infants with confirmed drug exposure who are asymptomatic or minimally symptomatic do not require pharmacologic therapy. Consistent scoring of signs of withdrawal enables decisions about the institution of pharmacologic therapy to be more objective and allows a quantitative approach to increasing or decreasing dosing. Studies of drug withdrawal, including therapeutic

approaches and outcomes, must ensure comparability of experimental groups by pretreatment and subsequent withdrawal severity scoring.

4. Pharmacologic therapy of withdrawal-associated seizures is indicated. Other causes of neonatal seizures also must be evaluated.
5. 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.
6. Drug selection should match the type of agent causing withdrawal. Thus, for opioid withdrawal, tincture of opium is the preferred drug; for sedative-hypnotic withdrawal, phenobarbital is the agent of choice.
7. Physicians should 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.
8. The use of naloxone in the delivery room is contraindicated in infants whose mothers are known to be opioid-dependent. However, in the absence of a specific history of opioid abuse, naloxone treatment remains a reasonable option in the delivery room management of a depressed infant whose mother recently received a narcotic.

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