Symptoms of neonatal drug withdrawal consist of: W = wakefulness; I = irritability; T = tremulousness, temperature variation, tachypnea; H = hyperactivity, high-pitched persistent cry, hyperacusia, hyperreflexia, hypertonus; D = diarrhea, diaphoresis, disorganized suck; R = rub marks, respiratory distress, rhinorrhea; A = apneic attacks, autonomic dysfunction; W = weight loss or failure to gain weight; A = alkalosis (respiratory); L = lacrimation (Fig 1); also, hiccups, vomiting, stuffy nose, sneezing, yawning, photophobia, twitching, myoclonic jerks, opisthotonus, or seizures.

When these symptoms are seen in a newborn infant, the physician should consider a diagnosis of withdrawal from maternal drugs. Narcotics reported to cause these symptoms in the neonate are heroin,1 methadone,2 meperidine,3 morphine,1 codeine,4 pentazocine,5,6 and propoxyphene.7 A glossary of drugs is provided in Fig. 2.

The onset of symptoms may be present at birth or may begin within four days of delivery. In some instances, symptoms may not become obvious until 10 days of age. This depends upon the drug the infant was exposed to in utero and the pharmacokinetic excretion of the drug. Subacute symptoms of narcotic drug withdrawal may last for 4 to 6 months.8 Rosen and Pippenger9 have demonstrated that infants born to mothers maintained on methadone do not begin to manifest withdrawal symptoms until the plasma level is less than 0.06 g/mL. In utero exposure to multiple drugs may cause a biphasic pattern of withdrawal symptomatology in the neonate.10 Polydrug abusers frequently use as many as two to five drugs in combination; these might include phenobarbital, diazepam, marijuana, pentazocine, triptelennamine, phencyclidine, and codeine.11 A physician who is unaware of a mother’s drug ingestion may initially make an erroneous diagnosis of colic in the infant; therefore, a detailed maternal drug history should be obtained, including prescription and nonprescription drugs received, social habits of the parents, and whether the mother is breast-feeding. In the event a negative drug history is obtained but infant symptomatology is consistent with drug withdrawal, a drug screen should be performed on the mother’s or infant’s blood and urine. Recently, screening of meconium for drugs has been reported to produce greater confirmation of fetal drug exposure than screening of urine.12

TREATMENT OF NARCOTIC WITHDRAWAL FROM MATERNALLY ACQUIRED DRUGS

Treatment of the neonate should be primarily supportive, as unjustified pharmacologic administration will prolong hospitalization and subject the infant to additional exposure to drugs that are not 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 symptomatology which might suggest another disease process taking place (ie, infection). The clinical symptoms in 30% to 50% of infants who manifest drug withdrawal may be treated in the above manner without use of pharmacologic therapy.

Excess weight loss may represent inadequate provision of calories rather than the need for pharmacologic therapy. Besides the caloric expenditure caused by increased activity, crying, and decreased sleep, calories may be lost through vomiting, drooling, and diarrhea. Hyde et al13 have shown that infants withdrawing from maternal narcotics have an increased O2 consumption at the tissue level, which increases caloric need. Caloric intake should be calculated daily in order to provide the 150 to 250 cal/kg/24 h necessary for proper growth in babies suffering withdrawal from narcotics.14,15

Each nursery should adapt one of the abstinence scoring methods to judge the need for drug therapy as nurses and doctors often become sympathetic with the jittery and frantic behavior observed in the infant and are prone to begin drug therapy for subjective reasons.16-18 An abstinence scoring sheet results in the use of more objective criteria for
that infection, hypoglycemia, hypocalcemia, hypomagnesemia, hyperthyroidism, CNS hemorrhage, and anoxia be ruled out as the etiology for the symptoms. The history of a drug abuser mother should be checked for evidence of past hepatitis or sexually transmitted disease.

PHARMACOLOGIC AGENTS USED TO TREAT NARCOTIC WITHDRAWAL

Narcotics

Paregoric. Many physicians prefer paregoric for therapy of the narcotic abstinence syndrome because of the ease in administration of the drug. Infants treated with paregoric for narcotic withdrawal symptoms have 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.\textsuperscript{19}

Paregoric contains anhydrous morphine (0.4 mg/mL). In addition, it contains opium alkaloids which consist of isoquinoline derivatives (narcotine and papaverine) which are antispasmodics and phenanthrene derivatives (morphine and codeine) which are analgesics and narcotics. Paregoric contains camphor, a CNS stimulant that 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 alcohol (44\% to 46\%), which is a CNS depressant, and anise oil, which may cause habituation. Benzoic acid (4 mg/mL), an oxidative product of benzyl alcohol, is present in paregoric. Severe acidosis, CNS depression, respiratory distress, hypotension, renal failure, seizures, and death have been reported to occur in small premature infants who receive benzyl alcohol in amounts of 99 to 234 mg/kg/24 h.\textsuperscript{20-22} Glycerine is another component.

The dose of paregoric administered to a full-term infant for treatment of neonatal narcotic withdrawal is from 0.2 mL (0.08 mg morphine equivalent) to 0.5 mL (0.2 mg morphine equivalent) per dose every 3 to 4 hours until the symptoms of withdrawal are controlled. A neonatal abstinence score is helpful in determining the need for increasing or decreasing the dose. The dose of paregoric should be tapered after symptomatology has been stabilized for three to five days.

Tincture of Opium. The United States Pharmacopeia preparation of tincture of opium also contains opiate alkaloids and morphine (10 mg/mL) but in a weaker alcohol preparation (17\% to 21\%). There is concern about stocking tincture of opium in hospital pharmacies because doctors and nurses may inadvertently mistake this preparation for paregoric and thus administer an excess dose of opium. A 25-fold dilution of tincture of opium contains the


determining when pharmacologic treatment is necessary and whether a drug dose should be advanced or decreased. 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.

Indications for drug treatment include vomiting and diarrhea that result in excessive weight loss or dehydration, inability of the infant to sleep, fever unrelated to infection, and seizures. It is essential that infection, hypoglycemia, hypocalcemia, hypomagnesemia, hyperthyroidism, CNS hemorrhage,
same concentration of morphine equivalent as paregic (0.4 mg/mL morphine equivalent) without the additives (camphor, anise oil, benzoic acid, or glycerine) found in paregic. A recent study has shown that the diluted solution remains stable for at least 2 weeks (S. Segal, unpublished data, 1983). Because of the danger of mistaking tincture of opium for paregic, tincture of opium should be dispensed to the nursery only in a dilution that contains a concentration of morphine equivalent to the concentration in paregic. A suggested name for the preparation is “neonatal opium solution.” Diluted tincture of opium should be administered according to the same morphine equivalent dosage schedule used for paregic.

**Morphine.** In the past, parenteral morphine has been used to treat the severe vasomotor collapse observed in infants with heroin withdrawal.15

The parenteral form of morphine contains sodium bisulfite (1 mg/mL), which has been reported to produce an anaphylactic reaction consisting of pruritus, flushing, and acute wheezing in older patients.24 The parenteral form of morphine also contains phenol (5 mg/mL). Absorption of phenol via the skin has been associated with jaundice in small infants.25 The dose of phenol that produces hyperbilirubinemia is not known. The 8-mg/mL ampul of morphine also contains 7 mg/mL (0.12 mEq/mL) of sodium chloride. Because morphine is used in such small doses, these additives may not have a significant effect on the infant.

An oral preparation of morphine (2 and 4 mg/mL), which contains no additives and less alcohol than paregic (10%), is now available. Oral morphine has less analgesic effect than the same parenteral dose. To date there have been no studies in which morphine preparations with morphine equivalents similar to paregic have 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 paregic.

There is some concern regarding safety in use of opiate preparations in neonates due to their marked respiratory depressant effect. This concern is accentuated in the report by Mitchell et al26 of life-threatening reactions in infants less than 3 months of age who were premedicated with morphine. They found that morphine doses of 0.1 mg/kg may cause respiratory cessation in non-narcotic-habituated infants. Infants manifesting narcotic withdrawal will be more refractory to this dose.

**Methadone.** The neonatal abstinence syndrome has been treated with methadone. The prolonged plasma half-life of methadone (t1/2 = 26 hours) makes difficult the adjustment of the dose of methadone in the infant during decreasing requirements.9 The multiple-dose vial of methadone contains chlorobutanol (0.5 mg/mL), which is a sedative, and 8% ethyl alcohol in the oral form.

**Neuroleptics**

**Diazepam.** Rapid suppression of narcotic withdrawal symptoms has been observed in infants treated with diazepam (1.0 to 2 mg every 8 hours). The newborn infant has a limited capacity to metabolize and excrete diazepam. Total elimination of diazepam and its metabolites may take 1 month or more.27 The infant’s suck reflex may also be depressed, and late-onset seizures have been observed in infants treated with diazepam.26 Parenteral diazepam contains benzyl alcohol (1.5%) and sodium benzoate (5%), which may displace bilirubin for conjugation and excretion; therefore, use of diazepam is contraindicated in a jaundiced infant or a premature infant.29 Nathenson et al30 measured albumin binding capacities of addicted infants treated with diazepam and found some decrease in albumin binding capacity.

In addition, parenteral diazepam contains ethyl alcohol (10%) and significant 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 h) of parenteral multivitamins which contain 30% propylene glycol.31,32

**Chlorpromazine.** The CNS and gastrointestinal symptoms produced by narcotic withdrawal are controlled by chlorpromazine. A dosage of 2.2 to 3 mg/kg/24 h in divided doses every 6 hours intramuscularly or orally has been used in infants. Occasionally, hypothermia may develop. The abnormalities in rapid eye movement (REM) sleep observed during withdrawal are not alleviated by chlorpromazine. Some chlorpromazine metabolites are eliminated slowly over an 18-month period in adults; therefore, a prolonged excretion time may be anticipated in the neonate.31 Chlorpromazine contains sodium chloride (6 mg/mL), sodium bisulfite, and sulfite (2 mg/mL). The multidose vial contains benzyl alcohol (2%).

**Sedatives**

**Phenobarbital.** Hyperactive behavior in the infant who manifests narcotic withdrawal is modified by administration of phenobarbital, but the drug does not relieve the gastrointestinal symptoms. Large doses of phenobarbital may significantly suppress the CNS of the infant, may impair the suck reflex, and may delay the bonding between mother and infant. Elixirs of phenobarbital contain 14% to 25% alcohol. The parenteral forms contain propyl-
ene glycol (67.8%), ethyl alcohol 10%, and benzyl alcohol 1.5%. The therapeutic blood level of phenobarbital necessary for control of narcotic withdrawal is not known. Finnegan et al\(^3\)\(^4\) used a neonatal loading dosage of 16 mg/kg/24 h of phenobarbital that produced blood levels of 20 to 30 \(\mu g/mL\), which effectively controlled symptoms of narcotic withdrawal.\(^3\)\(^4\) A blood level should be obtained 24 to 28 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 et al\(^3\)\(^4\) reported that maintenance doses of 2 to 8 mg/kg/24 h 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 level to decrease by 10% to 20% per day.

**Antihypertensive Agent**

Clonidine has been shown to reduce withdrawal symptoms in adult opiate addicts. It has been administered to two neonates withdrawing from maternal methadone.\(^3\)\(^5\) More data are required to define the role of clonidine in the treatment of neonatal withdrawal.

**GENERAL CARE OF THE NEONATE**

Medications should be administered at the time of feeding in order to limit the number of times the infant is disturbed. When vomiting is a problem, oral drugs may be administered 30 minutes before a feeding. After a stabilizing dose is attained, the drug dose should be maintained so that the infant sleeps well, eats effectively, and gains weight for a period of three to five days; then the dose may be tapered. The physician may be hesitant to taper the dose of medication; this hesitancy may result in prolonging the infant's hospitalization and drug therapy. The abstinence scoring sheet and changes in weight may be used to determine objectively the rapidity with which drug therapy should be tapered. Irritability and tremors should not be used as a criterion for continued drug administration as subacute symptoms of irritability, tremors, and poor sleeping patterns may last until age 6 months.\(^8\)

**FOLLOW-UP CARE**

Optimal treatment of the infant requires a team approach by a physician who is knowledgeable of the symptoms and therapy of neonatal withdrawal and who communicates with the parents; a nursing staff willing to tolerate the symptoms of the infant and willing to incorporate the parents into the total care of the infant; and a social service worker who can win the confidence of the parents and thus determine the parents' ability to care for the infant after discharge from the hospital.

The period of treatment in the hospital is the time when both parents learn to help care for their infant. The infant who is withdrawing from a drug is a very difficult infant with whom to bond and with whom to live on a 24-hour basis; the caretakers should be provided constant emotional support. Participation of the parents in the care of their infant in the hospital assists them in gaining confidence in interpreting the infant's symptoms and decreases the demands for medication sought for subacute symptoms of withdrawal once the infant is discharged from the hospital. No infant born to a known drug abuser should be discharged home on drugs as the parents may sympathetically use the drug for a longer period of time than is indicated or they may use the drug to supply their own need for drug replacement. Parents of infants who are withdrawing from drugs prescribed to the mother for medical purposes have strong guilt feelings and tend to overreact to the symptoms demonstrated by the infant.

Recurrence of withdrawal symptoms in the infant may develop after discharge from the hospital. It is essential that the hospital staff establish rapport with the parents so that they will return the infant to the hospital for treatment in this event. Sudden infant death syndrome (SIDS) and acquired immunodeficiency syndrome (AIDS) have been observed in infants born to methadone and heroin users.\(^3\)\(^6\)-\(^3\)\(^9\) In one study, the incidence of SIDS was correlated with the severity of the infants' withdrawal symptoms while in the nursery.\(^4\)\(^0\)

There should be a long-term follow-up of the physical and mental development of any infant who is withdrawing from maternal drugs.

**AGENTS PRODUCING SYMPTOMS SIMILAR TO THOSE OF NARCOTIC WITHDRAWAL**

Other maternal medications may produce in the infant a symptom complex similar to that of narcotic withdrawal (Table 1). The symptoms observed in the infant may represent withdrawal or intoxication and may last for variable periods of time (days to months).

In general, infants who demonstrate intoxication from maternal drugs require mostly supportive care during the period of excretion of the drug rather than administration of additional pharmacologic agents that the infant must metabolize and excrete. In cases of severe symptomatology, drug therapy may be indicated for patient comfort.

Infants who manifest adverse reaction to maternal psychotropic agents and who require pharma-
TABLE 1. Nonnarcotic Maternal Drugs That Cause Neonatal Psychomotor Behavior Consistent with That Produced by Withdrawal (W) or Intoxication (I)*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Symptoms</th>
<th>Duration of Symptoms</th>
<th>W/I</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Hyperactivity, crying, irritability; poor suck, tremors, convulsions, onset of symptoms at birth, poor sleeping pattern, hyperphagia, diaphoresis</td>
<td>18 mo</td>
<td>W</td>
<td>42–44</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Tremors, poor sleeping patterns, feeding difficulty, abdominal pain</td>
<td>9 mo</td>
<td>I</td>
<td>45</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Irritability, severe tremors, hyperacusis, excessive crying, vasomotor instability, diarrhea, restlessness, ↑ tone, hyperphagia, vomiting, disturbed sleep; onset 1st 24 h of life or at 10–14 d of age</td>
<td>4–6 mo-Rx</td>
<td>W</td>
<td>46–49</td>
</tr>
<tr>
<td>Bromide</td>
<td>Lethargy, dilated pupils, hypotonia, hyperreflexus, high-pitched cry, feeding difficulty, ↓ reflexes</td>
<td>2½ mo, 5 d-Rx</td>
<td>I</td>
<td>50,51</td>
</tr>
<tr>
<td>Chlordiazepo-ide</td>
<td>Irritability, tremors; symptoms may start at 21 d</td>
<td>9 mo, 1½ mo-Rx</td>
<td>W</td>
<td>52</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Extrapyramidal dysfunction, intention tremor, opisthotonos, mask-like facies; onset 1st 24–36 h</td>
<td>9 mo, 12 wk-Rx</td>
<td>I</td>
<td>41,53</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Hypothermia, cyanosis, tremors; onset 12 h of age</td>
<td>4 d-Rx</td>
<td>W</td>
<td>54</td>
</tr>
<tr>
<td>Desmethyli-</td>
<td>Breathlessness, cyanosis, ↑ HR, ↑ RR, diaphoresis, irritability, feeding difficulty, weight loss</td>
<td>10–30 d</td>
<td>I</td>
<td>55</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Hypotonia, poor suck, hypothermia, ↑ hypertonia, hyperreflexia, tremors, vomiting, hyperactivity, tachypnea, (mother multiple drug therapy)</td>
<td>8 mo, 10–66 d-Rx</td>
<td>I</td>
<td>56,57</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Tremulousness, diarrhea. Onset 5 d of age</td>
<td>9 d-Rx</td>
<td>I</td>
<td>58</td>
</tr>
<tr>
<td>Ethchlorvynol</td>
<td>??Lethargy, jitteriness, hyperphagia, irritability, poor suck, hypotonia, (mother receiving multiple-drug therapy)</td>
<td>10 d-Rx</td>
<td>I and W</td>
<td>59</td>
</tr>
<tr>
<td>Glutethimide</td>
<td>↑ tone, tremors, opisthotonos, high-pitched cry, hyperactive, irritable, “colic”</td>
<td>6 mo</td>
<td>W</td>
<td>60</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>Tremors, irritability, hyperactivity, jitteriness, shrill cry, myoclonic jerks, hypotonia, ↑ RR, ↑ HR, feeding problem, clonic movements (Mother receiving multiple therapy)</td>
<td>5 wk-Rx</td>
<td>W</td>
<td>61</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Cyanosis, respiratory distress, vasomotor instability, irritability, hypokinesia, convulsions, jerky movements, ↑ RR, autonomic dysfunction, hyperactivity, belly dance movements of abdomen before voiding</td>
<td>6 d</td>
<td>I</td>
<td>62</td>
</tr>
<tr>
<td>Lithium</td>
<td>Respiratory distress, lethargy, cyanosis, poor suck, hypotonia</td>
<td>10 d</td>
<td>I</td>
<td>63,64</td>
</tr>
<tr>
<td>Local anesthe-</td>
<td>Acidosis, convulsions, ↓ HR, opisthotonos, neurologic depression, apnea, spontaneous movement, ↓ responsiveness, ↑ reflexes, abnormal oculomotor reflexes, death, hypotonia, fixed pupils</td>
<td>Related to Rx, excreted by 1st 24 h</td>
<td>I</td>
<td>65–69</td>
</tr>
<tr>
<td>Magnesium sulpate</td>
<td>Respiratory depression, hypotonia, convulsions, death</td>
<td>Depends on Rx</td>
<td>I</td>
<td>70,71</td>
</tr>
<tr>
<td>Meprobamate</td>
<td>Irritability, tremors, poor sleep patterns, abdominal pain</td>
<td>9 mo, 3 mo-Rx</td>
<td>W</td>
<td>45</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>Jitteriness, hypertonia, vomiting, lethargy, vertical nystagmus</td>
<td>18 d + Rx, 8 da + Rx</td>
<td>I</td>
<td>72,73</td>
</tr>
<tr>
<td>Theophylline</td>
<td>↑ HR, gagging, vomiting, jitteriness, opisthotonos</td>
<td>2 d</td>
<td>I</td>
<td>74</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>? Late-onset, extrapyramidal dysfunction</td>
<td>9 mo, 2–3 d-Rx</td>
<td>I</td>
<td>53,57</td>
</tr>
</tbody>
</table>

* Abbreviations used are: HR, heart rate; RR, respiratory rate; Rx, refers to infant treated with pharmacologic agents and the natural course of the symptoms may have been shortened.
TABLE 2. Pharmacologically Active Excipients in Products Used to Treat Neonatal Withdrawal*

<table>
<thead>
<tr>
<th>Excipients</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anise oil</td>
<td>Tincture of paregoric (po)</td>
</tr>
<tr>
<td>Benzoic acid and sodium benzoate</td>
<td>Diazepam (P)</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>Tincture of paregoric (po)</td>
</tr>
<tr>
<td>Camphor</td>
<td>Diazepam (P)</td>
</tr>
<tr>
<td>Chlorobutanol</td>
<td>Methadone (P)</td>
</tr>
<tr>
<td>Ethyl alcohol</td>
<td>Morphine (P and po)</td>
</tr>
<tr>
<td>Opium alkaloids</td>
<td>Opiate tincture (po)</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>Tincture of paregoric (po)</td>
</tr>
<tr>
<td>Sodium bisulfite and sulfite</td>
<td>Diazepam (P)</td>
</tr>
</tbody>
</table>

* Abbreviations used are: P, parenteral; po, per os (by mouth).

**REFERENCES**


The information provided herein should serve as a guide for the physician in providing supportive care and pharmacologic treatment of the infant suffering from drug withdrawal.

**COMMITTEE ON DRUGS, 1982–1983**

Albert W. Pruitt, MD, Chairman
Walter R. Anyan, Jr, MD
Reba M. Hill, MD
Ralph E. Kauffman, MD
Howard C. Mofenson, MD
Harvey S. Singer, MD
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Sam A. Licata, MD
Godfrey Oakley, MD
Steven Sawchuk, MD
Louis Farchione, MD

AAP Section Liaisons
Earl J. Brewer, MD
John A. Leer, MD

**SUMMARY**

The Committee on Drugs of the American Academy of Pediatrics recommends that thoughtful consideration be given to the need for administration of pharmacologic agents to newborn infants who have symptoms of drug withdrawal. Supportive care should be the first line of therapy, and objective methods such as an abstinence scoring sheet should be used to determine the need for instituting and then discontinuing pharmacologic treatment. When appropriate, specific drug therapy should be used for treatment of withdrawal symptoms (ie, phenobarbital for phenobarbital withdrawal and opiate for opiate withdrawal). Attention should be given to potential adverse effects in the infant resulting from excipients present in many of the drugs (Table 2).

The information provided herein should serve as a guide for the physician in providing supportive care and pharmacologic treatment of the infant suffering from drug withdrawal.


23. Deleted in proof


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**A DIFFERENCE IN THE FAMILY**

Sometimes outsiders accept [a disabled] child but expect unreasonable sacrifices of his parents. Lucy Forrest described ... the ways that neighbors and strangers helped her and her husband implement a demanding treatment plan for Christopher. Volunteers came in daily to 'pattern' the little boy; contributions helped the family finance bimonthly trips to a distant clinic. But this support given freely during the early months when the Forrests devoted every minute to their baby, almost evaporated when they started to pick up the threads of their previous life. Specifically, when Lucy began to repaper their new house, some of the volunteers acted shocked and even hostile. The reaction wounded the young couple; they felt the world exacted a heavy price for its sympathy, asking that they devote their entire lives to their hurt son and give up the pleasures others take for granted.

Submitted by Student

Neonatal Drug Withdrawal

*Pediatrics* 1983;72:895

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