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Early Treatment for Neonatal Abstinence Syndrome: A Palliative Approach

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Abstract

Objective To describe medical, safety, and health care utilization outcomes associated with an early treatment model for neonatal opioid withdrawal.

Study Design This is a retrospective review of 117 opioid-exposed infants born in a large regional hospital and treated in the level I nursery with methadone initiated within 48 hours of birth.

Results For this cohort, mean length of stay was 8.3 days. Hospital safety events were infrequent; there were no medication errors or deaths. Within 30 days of discharge, 14% of infants visited the emergency department; 7% were readmitted. Per birth, mean hospital charges were $10,946.96; mean costs were $5,908.93.

Conclusion This study is the first to describe an early treatment model in a low-acuity nursery to prevent severe neonatal opioid withdrawal. The described model may be safe, effective, low-cost, and feasible for replication.

Because of increasing opioid use among pregnant women,1 the incidence of neonatal abstinence syndrome (NAS) in the United States rose from 3.4 to 5.8 per 1,000 hospital births between 2009 and 2012,2 and the condition has been labeled a national epidemic. Because a significant proportion of cases are treated in intensive care nurseries,3 the cost of hospitalization for full treatment and weaning using the conventional approach is high. Between 2000 and 2012, U.S. mean hospital charges for a newborn with NAS increased from $39,400 to $66,700, with Medicaid as the primary payer.2,4

In a 2000–2007 national study of opioid use during pregnancy among Medicaid-enrolled women, Desai et al reported that 21% of women filled an opioid prescription during pregnancy.5 In a 2005–2011 study utilizing a national sample of privately insured women, Bateman et al reported the prevalence of any opioid use anytime during pregnancy to be 14.4%.6 Little information exists about opioid use among pregnant women entering substance use treatment programs7; however, for 19% of pregnant and nonpregnant women, opioids are the primary substance misused.8 Methadone has been widely accepted for use in pregnant women with opioid use disorders since the 1970s.9,10 Since 1998, methadone has been the recommended standard of care for this population.11 Medical maintenance treatment with methadone has the same benefits for pregnant patients as for patients in general. Comprehensive maintenance treatment including prenatal care significantly reduces neonatal morbidity and mortality12; however, it also raises the risk for

Keywords
► buprenorphine
► cost-effective
► early treatment
► fetal opioid exposure
► methadone
► neonatal abstinence syndrome
► neonatal drug withdrawal
► neonatal opioid withdrawal

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neonatal opioid withdrawal. According to the Tennessee Department of Health’s 2015 NAS surveillance report, more than half of cases statewide were attributable to supervised opioid replacement therapy. These data are consistent with earlier sources that estimated NAS prevalence at 48 to 95% in neonates born to women in opioid maintenance treatment. Therefore, care models focused on infants born to mothers in recovery may be able to address a significant proportion of NAS cases.

The conventional approach to managing NAS holds great challenges. No formal national guidelines for managing NAS yet exist, but standard practice is to delay pharmacotherapy until a newborn displays sufficient objective signs and symptoms to justify treatment. This practice is based on several influences: NAS signs vary considerably and depend on several factors; some infants may be adequately managed with nonpharmacologic care; pharmacotherapy is typically administered only in high-acuity settings; withdrawal is believed to be a self-limited process and has undefined long-term morbidities; and studies suggest that prolonged fetal opioid exposure may cause harm. In past decades, developing recommendations for pain management in neonates was similarly challenging. Pain symptoms in neonates are likewise nonspecific and vary considerably. There is no way to define the degree of pain that specific minor or major procedures will cause for a specific infant. However, research now supports the concept that pain experiences in neonates have the potential to cause harm, and the prevention and effective management of pain should be a goal of those caring for at-risk neonates. Because neurologic pathways for pain and withdrawal are similar, methods for managing NAS should achieve a similar goal.

New models for treating confirmed NAS have been described that support expanding beyond conventional approaches. Patrick et al reported that methadone as initial treatment was associated with reduced hospital stay and duration of opioid therapy. Backes et al demonstrated that a combined inpatient and outpatient treatment model reduces hospital stay and costs. Johnston et al recommended methadone for pharmacologic treatment and outlined a standardized approach for inpatient care and outpatient weaning. A model of prevention has not yet been explored. Hudak et al described the concept that “each clinical unit can establish a threshold level of cumulative [iatrogenic] exposure to opioids... above which drug dependency can be expected to occur with a likelihood that justifies anticipatory initiation of a weaning protocol.” In the same way, continuous fetal opioid exposure due to placental transfer of maternal long-acting opioid therapy in late gestation may also justify initiation of a weaning protocol immediately after birth. According to Hall’s multicenter cohort study of outcomes related to NAS, the mean onset of symptoms was 46.1 hours of age, which is consistent with other reports in the literature. At its peak, withdrawal is difficult to manage. By the time symptoms are controlled with pharmacotherapy, significant suffering and physical effects have often already occurred. These are well-documented to include excessive weight loss, feeding problems, self-inflicted excoriations, perianal maceration, vomiting, diarrhea, dehydration, and disruption of bonding and breast-feeding. Supportive therapies such as high-calorie feedings, intravenous fluids, treatments for perianal skin breakdown, therapies for hypertonicity, and disorganized feeding patterns may be needed to reverse the physical effects that occurred while waiting for enough objective evidence to rationalize pharmacotherapy. If withdrawal leads to newborn fever, additional blood work, procedures, and intravenous antibiotic treatment may be added. Therefore, delayed treatment may contribute to longer hospitalization, and medical complications of withdrawal must be addressed. The objective of this study was to describe medical, safety, and health care utilization outcomes associated with an early treatment model for neonatal opioid withdrawal.

Patients and Methods

This study is a descriptive analysis of newborns at high risk for opioid withdrawal who were treated with early methadone (within 48 hours) in a level I newborn care setting during 2006 to 2014. The study hospital is a large, regional perinatal referral center containing 710 beds with an average annual volume of 5,221 births from 2006 to 2014. This hospital is part of a public, not-for-profit academic health care delivery system. Approval from institutional review board was obtained prior to the study. Data collection was performed through data extraction from electronic medical records and direct chart review. All data were abstracted by a trained research assistant. The standard definition for an NAS birth was established prior to abstraction as ICD-9 code(s) 779.5 and/or 760.72. The exclusion criteria were admitted to neonatal intensive care immediately after birth, methadone not administered within 48 hours, and transfer to intensive care for complications or illness prior to completion of the treatment model.

Analysis of outcomes related to health, safety, health services utilization, and cost was conducted. Descriptive statistics (frequency, percent, mean, median, range, and standard deviation [SD]) were generated using Stata 14 (StataCorp, College Station, Texas). Results are presented as mean (SD) if not otherwise indicated. Primary outcome measures included hospital length of stay; need for adjunctive medication; medical complications requiring transfer to a higher level of care; adverse medication and safety events; readmission rates; and total hospital charges, cost, and revenue per case.

Early Treatment Model Description

The early treatment model, developed in 2003, is based on the theory that neonates chronically exposed to long-acting opioids in late gestation are born in steady state. Research has demonstrated significant transfer of opioids across the placenta. When started within 24 hours of birth, methadone may be considered a continuation of therapy and prevent severe opioid withdrawal and its complications. The model was developed by a multidisciplinary team, including representatives from pediatric and developmental medical staff, pediatric pharmacy, nursing administration, nursing staff,
social work, physical and occupational therapies, and child advocacy. The literature supports that 55 to 94% of neonates with chronic fetal exposure to long-acting opioids will experience clinically significant withdrawal.\(^{21}\) For the small percentage of newborns who may receive unnecessary pharmacologic therapy under the early treatment model, the team decided to ensure that infants are formally screened for vital sign changes and symptoms of oversedation during hospitalization.

The original model evolved over the course of a decade. Early changes included the development of preprinted order sets, changing a mandated 10-day stay for all at-risk newborns to a length of stay driven by medical need, an option for mothers to room-in for the entire newborn stay, and selection of methadone as the preferred pharmacotherapy to prevent severe opioid withdrawal. Additional changes included assignment of all newborns discharged on medication to one pediatric medical home for the duration of weaning, dispensing methadone in prefilled oral syringes, changing a requirement for caregivers to complete infant cardiopulmonary resuscitation (CPR) training prior to discharge to providing caregivers with formal education about safe sleeping environments, and recommending community-based infant CPR classes. Structure was added to the outpatient weaning process, with a target wean of 30 days and 15% dose reductions on prescribed days.

Currently, infants admitted to the mother/baby unit whose mothers are taking chronic long-acting opioids are offered early treatment, breast-feeding support (unless contraindicated), and extended stay for the hospitalization. Potential risks and benefits of early treatment are reviewed with parents; they are allowed to decline but are informed of symptom thresholds that will require pharmacotherapy during the birth hospitalization. All neonates deemed to be at risk for withdrawal are managed by a newborn hospitalist and receive low-stimulation supportive care. Infants exposed to maternal methadone doses of 60 mg or higher are started on 0.1 mg/kg/dose every 6 hours; those exposed to less methadone or buprenorphine are started on 0.05 mg/kg/dose every 6 hours. A pediatric pharmacist is involved with all cases for dosing recommendations and development of the weaning calendar. Urine and meconium drug screening and prescription monitoring database queries are routinely performed. To address the concern that a small percentage of neonates administered early methadone may be overtreated, continuous pulse oximetry is initiated, methadone is held until symptoms resolve, and then methadone is restarted at a lower dose or increased interval. For poor symptom control, methadone dosing is increased by 0.05 mg/kg approximately every 36 to 48 hours, to a maximum of 0.2 mg/kg/dose. Once abstinence scores are consistently eight or lower for 36 to 48 hours, the methadone interval is changed to 8-hour dosing, maintaining the same total daily dose. After another 36 to 48 hours with stable scores, the methadone interval is changed to 12-hour dosing, maintaining the same total daily dose. After a final 36 to 48 hours with stable exams, scores, vital signs, and weight, the infant is discharged to an appropriate caregiver for outpatient weaning. All infants are discharged on methadone. A weaning calendar is developed by a pediatric pharmacist, and methadone is dispensed in prefilled oral syringes from the hospital outpatient pharmacy, which has an average out-of-pocket cost of $13. Caregivers are required to fill the prescription prior to discharge, and unit staff personnel reconcile that all needed syringes have been dispensed and that caregivers understand how to administer medication per the calendar. Apnea/bradycardia monitoring and abstinence scoring are discontinued at discharge.

Dosage reductions of approximately 15% (of the discharge dose) occur every Sunday and Wednesday. Office visits occur at the outpatient pediatric medical home weekly during weaning to evaluate the effect of medication reduction. Outpatient physicians assess for signs or symptoms of poor NAS control and slow down the weaning process if necessary. One or two home nursing visits are provided through the regional health department office. Families are educated about signs of uncontrolled withdrawal that should prompt additional visits; they are not asked to do formal scoring. All newborns are referred for formal developmental assessment at 3 or 4 months as well as to phone-based parenting support and developmental screening services (Help Me Grow, Greenville, SC) that are available to up to age 8.

**Results**

From 2006 to 2014, early methadone treatment was provided for 143 infants within 48 hours of birth. After early methadone administration, 26 infants were transferred to neonatal intensive care for medical illness or complications including fever \((n = 10; 38\%\)\), hypoglycemia \((n = 7; 27\%\)\), respiratory distress \((n = 6; 23\%\)\), supraventricular tachycardia \((n = 1; 4\%\)\), bilious emesis \((n = 1; 4\%\)\), and feeding difficulty \((n = 1; 4\%\)\). In the level 1 nursery, 117 newborns completed the early treatment model. Cohort selection criteria are detailed in —Fig. 1. —Tables 1 and 2 outline the demographic and clinical characteristics of mothers and their newborns in the studied cohort. Data tables for maternal characteristics reflect each pregnancy or birth separately.

Mean gestational age for newborns was 39 (SD: 1.6) weeks; mean birthweight was 2,940 (SD: 465) g. Among mothers, mean age was 28 (SD: 5.2) years, and 97% of mothers received prenatal care, with a mean of 8.3 visits per pregnancy. Four planned adoptions occurred. More than half of mothers reported chronic mental health issues (—Table 2). The
reported categories are not mutually exclusive; for example, 29 mothers experienced both depression and anxiety, and 11 mothers experienced bipolar disorder and anxiety.

Mothers taking buprenorphine reported an average daily dose of 14 (SD: 7) mg, and mothers taking methadone reported an average daily dose of 96 (SD: 50) mg. Mothers used medically assisted treatment for a variety of reasons: addiction to illegal substances (25%), addiction to nonprescribed opioids (46%), and dependence on/addiction to prescription opioids for acute (20%) or chronic pain (19%).

Maternal use of other drugs was measured through self-report as well as through infant urine and meconium drug screens. Illicit drug use during the third trimester triggered child protective services involvement but was not an exclusion criterion for the early treatment model. Nine (8%) mothers admitted illicit drug use after the first trimester. Newborn urine drug screens were confirmed positive for amphetamines in one infant and cocaine metabolites in two infants at delivery. Meconium drug screens were confirmed positive for amphetamines in one infant, methamphetamine in one infant, and cocaine metabolites in three infants.

Table 3 summarizes medical and safety outcomes for newborns treated with the model.

Forty-two percent in the cohort were fed breast milk; only 14 newborns required high-calorie supplementation. None experienced dehydration or a need for intravenous fluids. Adverse hospital events were infrequent; there were no medication errors and no deaths.

Seventy-five percent of patients met the targeted 30-day outpatient wean after its implementation during 2012. Seven patients visited the emergency department (ED) within 30 days of discharge and were not readmitted to the hospital. Two presented with symptoms possibly NAS-related: one medication issue and one diarrhea. Five of the discharged patients presented with symptoms not related to NAS; they were oral candidiasis, oral and diaper candidiasis, motor vehicle accident, minor head injury, and Listeria bacteremia (diagnosed after ED release). Nine patients were readmitted to the hospital within 30 days of discharge; six were for possible NAS-related issues, which included an event related to gastroesophageal reflux, feeding problems, failure to thrive, fever with NAS symptoms, and NAS symptoms alone. Three were readmitted for conditions not related to NAS.

Fig. 1 Cohort selection criteria. Retrospective chart review began with 472 newborn charts coded for withdrawal. Charts were excluded if the newborn was admitted to intensive care immediately after birth, not administered methadone before 48 hours of age, or required transfer to intensive care prior to discharge. In the level I newborn care setting, 117 patients completed the full early treatment model.
hypothermia, pertussis, and respiratory syncytial virus with urinary tract infection.

All hospital charge, cost, and revenue data were adjusted for inflation in 2014 USD. Per birth, mean total hospital charges were $10,946.96; mean total hospital costs were $5,908.63; and mean total revenue was $5,260.82. Mean length of stay per case was 8.3 days. Reported figures do not include any outpatient fees, ED charges, or physician fees incurred after discharge.

Discussion

Signs and symptoms of newborn opioid withdrawal have been well described in the literature and are consistent with phases of methadone withdrawal reported in adults. After 1 to 3 days of abstinence, subjective symptoms of withdrawal include fatigue, nausea, craving, irritability, depression, muscle aches, and wakefulness. After 3 to 5 days of abstinence, severe symptoms and objective signs manifest, such as involuntary muscle spasms, arthralgias, muscle and bone pain, vomiting, diarrhea, insomnia, fever, sneezing, yawning, and agitation.

In recent decades, increased attention has been given to preventing pain in neonates. According to the American Academy of Pediatrics (AAP), “The prevention of pain is important not only because it is an ethical expectation but also because repeated painful exposures can have deleterious consequences,” including long-term disabilities. In addition, the AAP reports that “early and effective pain treatment is associated with a lower total dose of medication” and fears that analgesics (especially opioids) may lead to hypotension or respiratory depression has never been confirmed in randomized controlled trials. According to Anand regarding the management of mild to moderate pain in neonates, “The use of environmental therapies (swaddling, sucrose, pacifiers) and decreased stimuli have limited therapeutic efficacy.” No reported treatment models for NAS have focused on the prevention of suffering associated with the experience. In contrast, experts to date have emphasized that newborn withdrawal is “a self-limited process” and have de-emphasized the importance of treating suffering until clearly measurable.

The concept of weaning pediatric patients with opioid dependence is not new. For those requiring prolonged life support and opioid therapy, standard practice is to wean opioids slowly over days to weeks to avoid the experience of withdrawal and symptoms that may confuse a complex medical course. Until now, this concept applied to fetal opioid dependence has never been studied.

While NAS treatment commonly occurs in the intensive care setting, there has been increased interest in lower-acuity settings.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Newborn demographic and clinical characteristics (n = 117)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency (n)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>59</td>
</tr>
<tr>
<td>Female</td>
<td>58</td>
</tr>
<tr>
<td>Race</td>
<td></td>
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<tr>
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<td>105</td>
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<tr>
<td>Hispanic, Latino, or Spanish origin</td>
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<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>2</td>
</tr>
<tr>
<td>Two or more races</td>
<td>6</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td></td>
</tr>
<tr>
<td>35–36</td>
<td>12</td>
</tr>
<tr>
<td>37</td>
<td>23</td>
</tr>
<tr>
<td>38–42</td>
<td>80</td>
</tr>
<tr>
<td>Apgar score at 5 min ≥ 8</td>
<td>115</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>20</td>
</tr>
<tr>
<td>Insured by SC Medicaid</td>
<td>111</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Maternal demographic and clinical characteristics (n = 117)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency (n)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>108</td>
</tr>
<tr>
<td>Black or African American</td>
<td>3</td>
</tr>
<tr>
<td>Two or more races</td>
<td>2</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
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<tr>
<td>Married</td>
<td>41</td>
</tr>
<tr>
<td>Never married</td>
<td>55</td>
</tr>
<tr>
<td>Divorced or widowed</td>
<td>16</td>
</tr>
<tr>
<td>Primigravida</td>
<td>21</td>
</tr>
<tr>
<td>Smoking during pregnancy</td>
<td>87</td>
</tr>
<tr>
<td>SSRI use during pregnancy</td>
<td>8</td>
</tr>
<tr>
<td>Benzodiazepine use during pregnancy</td>
<td>37</td>
</tr>
<tr>
<td>Opioid used during pregnancy</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>96</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>21</td>
</tr>
<tr>
<td>Mental health diagnosis (not mutually exclusive)</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>49</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>43</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>15</td>
</tr>
<tr>
<td>Postpartum depression</td>
<td>7</td>
</tr>
<tr>
<td>Posttraumatic stress disorder</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviation: SSRI, selective serotonin reuptake inhibitor. A cohort of 108 mothers gave birth to 117 studied infants. One mother had twins, and eight mothers had two infants at different times during the study period. White mothers were 96%, 71% completed high school, and 38% were married.
and community-based intervention strategies.\textsuperscript{17,34,35,42–44}

The 8.3-day mean hospital stay for our sample was less than half of that reported nationally for all NAS infants (mean: 16.9 days)\textsuperscript{2} and was approximately one-third the hospital stay for pharmacologically treated NAS infants (mean: 23 days).\textsuperscript{2}

Despite the significant reduction in stay, adverse safety and medical events for our studied cohort were low. Lee et al reported similar low rates of complication for a combined inpatient/outpatient model.\textsuperscript{42}

In the studied cohort, early treatment for newborns with significant opioid exposure during late gestation promoted early control of NAS symptoms without excessive risk of oversedation. Appropriate monitoring was effectively accomplished in a low-acuity setting; there were no reports of oversedation after discharge.

Patients displayed peak NAS symptoms consistent with the timing reported in other studies.\textsuperscript{3,19–21,36–38} The researchers hypothesize that early treatment kept newborns from entering severe opioid withdrawal, when most gastrointestinal symptoms manifest. The average infant did not experience significant feeding problems, excessive weight loss, diarrhea, dehydration, or severe perianal maceration.

### Table 3 Newborn outcomes (n = 117)

<table>
<thead>
<tr>
<th>Medical outcomes</th>
<th>Median (range)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay (d)</td>
<td>8 (4–18)</td>
<td>8.3 (2.7)</td>
</tr>
<tr>
<td>Peak weight loss (%)</td>
<td>7 (1–14)</td>
<td>7 (2.5)</td>
</tr>
<tr>
<td>Day of peak weight loss</td>
<td>4 (1–8)</td>
<td>3.7 (1.5)</td>
</tr>
<tr>
<td>Peak modified Finnegan score</td>
<td>10 (3–21)</td>
<td>10.4 (3.6)</td>
</tr>
<tr>
<td>Day of peak score</td>
<td>2 (0–7)</td>
<td>2.6 (1.7)</td>
</tr>
<tr>
<td>Methadone discharge dose (mg/kg/d)</td>
<td>0.4 (0.1–1.4)</td>
<td>0.5 (0.3)</td>
</tr>
<tr>
<td>Duration of outpatient methadone wean\textsuperscript{a} (d)</td>
<td>46 (10–96)</td>
<td>44.6 (16.3)</td>
</tr>
<tr>
<td>Cumulative methadone dose during outpatient wean\textsuperscript{b} (mg)</td>
<td>30 (3.1–160)</td>
<td>33.3 (25.4)</td>
</tr>
<tr>
<td>Need for adjunctive medications</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Prominent inpatient gastrointestinal symptoms</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Prominent inpatient central nervous system symptoms</td>
<td>60</td>
<td>51</td>
</tr>
<tr>
<td>Safety outcomes</td>
<td>Frequency (n)</td>
<td>Percent (%)</td>
</tr>
<tr>
<td>Inpatient adverse events</td>
<td>Frequency (n)</td>
<td>Percent (%)</td>
</tr>
<tr>
<td>Unsafe sleep practices</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Newborn oversedation</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Near suffocation</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Fall or drop</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Outpatient adverse events\textsuperscript{c}</td>
<td>Frequency (n)</td>
<td>Percent (%)</td>
</tr>
<tr>
<td>Alteration of planned wean after discharge</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Suspected mishandling of medication by caregiver</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Lacked medication to complete wean, no mishandling suspected</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>CPS involvement (not mutually exclusive)</td>
<td>Frequency (n)</td>
<td>Percent (%)</td>
</tr>
<tr>
<td>No involvement</td>
<td>60</td>
<td>51</td>
</tr>
<tr>
<td>Case opened antenatally or during hospitalization</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>Case opened after hospital discharge\textsuperscript{c}</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>Placement with foster family after discharge\textsuperscript{c}</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>Emergency services use\textsuperscript{c}</td>
<td>Frequency (n)</td>
<td>Percent (%)</td>
</tr>
<tr>
<td>ED visit or readmission with 30 d of discharge</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Possibly NAS-related</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Not NAS-related</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviations: CPS, child protective services; ED, emergency department; NAS, neonatal abstinence syndrome; SD, standard deviation.

\textsuperscript{a}Data on duration of outpatient wean available for 102 patients.

\textsuperscript{b}Data on cumulative dose available for 89 patients.

\textsuperscript{c}Data on outpatient events available for 115 patients.

and a majority did not require high-calorie feedings. Short
length of stay was attributed to early symptom stabilization
and related low rates of NAS complications.

One common argument against early methadone treat-
ment is a theoretical risk that longer durations of opioid
exposure may cause harm to the immature brain.7,8 New-
borns of mothers taking chronic opioids, however, have been
exposed to significant opioid levels for the entire duration
of fetal life. No studies have examined the long-term impact
of the experience of severe withdrawal on the neonatal brain
or human development.45 Several studies of methadone effects
on the fetal brain report developmental concerns but do
not examine whether deficits were related to medication
exposure, damage induced by the process of withdrawal, or a
combination. Although the ethical benefits of extending
opiod exposure to provide a gentle withdrawal process
have been discussed in the literature, the medical risks
and benefits have not been examined.

Research on NAS has documented the related and increasing
costs of treating affected newborns.2,4,42 With substantial fund-
from the state Medicaid, the cost of treatment is a concern
for a wide range of public and private stakeholders. The mean
total charges per birth for the cohort who completed the early
treatment model were $10,946.96. These charges are signific-
antly lower than the average U.S. 2012 charges reported to be
$66,700 per NAS case and $93,400 per inpatient pharmaco-
logically treated NAS case.2 Mean reimbursement per case in our
cohort was 48% of charges and resulted in an average net loss of
$647.82. Comparison of charge and length of stay data with that
reported nationally can be misleading, because several new-
borns with NAS might not qualify for an early treatment model
or may require intensive care for reasons other than withdrawal.
However, if data on the exposure source reported by Tennessee’s
Department of Health is generally representative of national
trends, more than half of all NAS cases may be associated with
supervised opioid replacement therapies.13 While our study did
not include a matched cohort for comparison, further analysis of
state data to identify a comparison group with the same exclu-
sion criteria is being performed and will be reported in a future
publication. Our study demonstrates that pharmacologic treat-
ment can be provided in a combined inpatient/outpatient setting
that results in reduced length of stay, maternal-infant separation,
and cost, without sacrificing safety or readmission rates.

Strengths of the current study included a consistent and
stable provider team over the course of model utilization,
development of a database for tracking adverse events and
related medical outcomes, and having an outpatient medical
home willing to provide standardized care for all discharged
patients. Potential limitations of this study included lack of a
control group, low numbers of neonates qualifying for the
early treatment protocol, adjustments made to the treatment
protocol over time, and an inability to define total opioid
exposure levels for the cohort. Of these, the most important
limitation was the fact that minor adjustments were made to
the treatment protocol over time. For example, standardized
weaning of 30 days or less was not implemented until 2012.
Prior to 2012, the pharmacists were not directed to limit the
length of the outpatient wean. As a result, the average
duration of treatment for the cohort was longer than the
duration for infants being treated with the model today. There
were several cases of suspected medication mishandling
during the early years of our treatment protocol, all of which
occurred when newborns were sent home with medication in
a multidose bottle. Such events did not occur after the change
to dispensing prefilled oral syringes. Although protocol changes
had the potential to impact results, the changes were each designed to improve the quality of care and address
protocol weaknesses that were observed over time. A barrier
to replication of our treatment model may be a variation in
state laws related to allowable methadone prescribing.

Future research may include a prospective study with a
comparison group to determine the effectiveness of this inter-
vention in other regional hospitals with low-acuity nurseries. If
similar results are demonstrated, the model may be a safe and
effective tool for improving clinical outcomes for newborns
diagnosed with NAS. In addition, maintaining a database of
newborns with mild to moderate NAS who were treated with
early methadone may allow for future reporting of associated
long-term medical, developmental, and family outcomes.

Conclusion
This study is the first to describe an approach to preventing
severe newborn opioid withdrawal using an early treatment
model. New models of care for NAS are needed; approaches
shown to be safe, effective, ethical, and economical have
widespread applicability. Establishing a viable model of
care for NAS treatment in low-acuity nurseries will provide
economic and social benefits to this unique population of
patients in our community, state, and nation. Demonstrating
a reduction in health care costs using our model could impact
health policy and professional guidelines yet to be developed.
Further, our model is family- and patient-centered, promot-
ing education, engagement, and empowerment of families
during the course of treatment. It is hoped that in the long
term, the model will impact overall family success.

Conflict of Interest
None.

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