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# Models of care for neonatal abstinence syndrome: What works?

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ABSTRACT

Opioid use disorders and the prescription of long-acting medications for their treatment have increased dramatically over the last decade among pregnant women. Newborns who experience prolonged in utero opioid exposure may develop neonatal abstinence syndrome (NAS). Until recently, much of the focus on improving care for NAS has been on pharmacologically-based care models. Recent studies have illustrated the benefits of rooming-in and parental presence on NAS outcomes. Single center Quality Improvement (QI) initiatives demonstrate the benefits of non-pharmacologic care bundles and symptom prioritization in decreasing the proportion of infants pharmacologically treated and length of hospital stay. Little remains known about the impact of these varied cared models on maternal-infant attachment and mental health. In this review article, we will propose an optimal model of care to improve short- and long-term outcomes for newborns, their mothers and families, and perinatal care systems.

## 1. Background

Opioid use and misuse, and medication-assisted treatment (MAT) for opioid use disorders (OUD), have increased dramatically over the last decade, including among pregnant women [1–3]. Newborns who experience prolonged in utero opioid exposure may develop neonatal abstinence syndrome (NAS) [4–8]. Rates of NAS, also known as neonatal opioid withdrawal syndrome (NOWS), have grown nearly fivefold over the past decade [9–11].

Although NAS is self-limited, its expression is variable. For infants exposed to methadone and buprenorphine, long-acting opioid replacement medications used for MAT, NAS typically peaks on the third or fourth days of life [12]. As symptoms can be further delayed in some infants [13], the American Academy of Pediatrics (AAP) recommends 4–7 days of postnatal observation [4]. For the subset of newborns with NAS symptoms severe enough to warrant pharmacologic treatment with opioid replacement medication, hospital length of stay (LOS) can be prolonged. In 2012, the average opioid-exposed infant had a LOS of 16 days, and the pharmacologically treated subset remained hospitalized for 23 days [10,14]. LOS varies by center, medication used for treatment, and polysubstance exposure [10,15,16].

An estimated 1.5 billion dollars were spent on NAS care in the United States (U.S.) in 2012 with mean inpatient costs of $93,400 per newborn [9,10]. Costs are largely driven by Neonatal Intensive Care Units (NICUs) [17–19]. By 2012, U.S. NICU admissions for NAS accounted for 4% of all NICU bed-days [19]. Variation in NAS care is common in NICUs and other settings, and likely contributes to increased costs and variable outcomes [17,20–22].

In this article, we will review various components of NAS care and the efficacy of different models of care for opioid-exposed newborns. Then, we will propose an optimal model of care that could improve outcomes for newborns, mothers and families, decrease unnecessary variation, control costs, and limit systemic strains on perinatal care systems.

## 2. Scoring and assessment

### 2.1. The Finnegan Neonatal Abstinence Syndrome Scoring Tool (FNAST)

The most common model of care for opioid-exposed newborns over the past 40 years is centered on the Finnegan Neonatal Abstinence Scoring Tool (FNAST) [17,18,23]. The FNAST was developed in the early 1970s by Dr. Loretta Finnegan and colleagues as a research tool to systematically assess the most common symptoms of opioid withdrawal

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and to monitor responses to treatment. In a standardized training program designed to promote inter-observer reliability among staff using the FNAST, initiation or escalation of pharmacotherapy is recommended for three consecutive symptom scores ≥8 or 2 scores ≥12 [24]. Although the FNAST demonstrated robust inter-rater reliability with its original development [23] and is recognized for its clinimetric properties [25], optimal scores for pharmacologic treatment initiation, adjustment, or discontinuation have not been established. A review of the original study reveals that the '8' threshold was chosen based on the researchers' clinical experience: "The infant with a score of '7' or less was not treated with drugs for the abstinence syndrome because, in our experience, he would recover rapidly with swaddling and demand feedings. Infants whose score was '8' or above were treated pharmacologically." [23] Although most non-opioid exposed newborns score < 8, a score of 7 is in the 95th percentile [26], meaning that 5% of unexposed newborns could be eligible for NAS pharmacotherapy based on established FNAST treatment criteria [24].

Although most hospitals report using 3 scores ≥ 8 or 2 scores ≥ 12 to initiate pharmacologic treatment, variation exists [17,18]. Concerns expressed regarding the FNAST have included the subjective nature of certain tool items, inconsistencies in scoring when staff are not formally trained, length and complexity of a research instrument used for clinical care, and poor psychometric properties [27]. Families report anxiety due to score-based thresholds. They find it stressful and disruptive to infants, noting discrepancies between care providers [28,29]. Parents and nursing staff express concern that the scored symptoms are not specific to NAS, as some symptoms are also seen in "normal" or non-opioid exposed infants [26]. Additionally, it is important to recognize that the FNAST was developed to monitor opioid-exposed newborns [23] and was not designed to assess effects of other in-utero substance exposures.

### 2.2. Modifications of the FNAST and of its use

Different FNAST score thresholds affect the chances an infant will be prescribed medication. In a retrospective study of 146 methadone-exposed newborns, 73% of infants would meet criteria for morphine treatment with a single score ≥9 as a threshold, while only 26% would be treated for 3 scores ≥9 (or 2 ≥ 12) [30]. Several studies have compared abbreviated, or modified, symptom assessment scales with the FNAST with the aim of finding a more efficient, effective, or easier system [27,31–33]. Though these alternative systems typically correlate with the FNAST [31] and may help differentiate between infants needing and not needing pharmacologic treatment [34], they have not been widely adopted into clinical practice [17].

Additionally, some centers have developed methods of score prioritization, using the FNAST, or a modification of it, to obtain the infants score and then prioritize the symptoms most problematic for the infant to aid in decisions around the initiation of pharmacotherapy [35,36].

The most significant limitation in this literature is that all measured outcomes relate to short-term outcomes associated with newborn hospitalization. There are no data available on the long-term outcomes of these different care approaches to symptom assessment or different thresholds for neonatal pharmacotherapy.

### 2.3. Alternative assessment approaches

Several prospective cohort studies have attempted to identify a more physiologically relevant assessment approach to identify newborns who might benefit from (or respond to) pharmacotherapy for NAS, but parameters such as maternal vagal tone [37], neonatal heart rate variability [38,39], skin conductance [40,41], and pupillary size [42] have failed to be adopted into clinical practice. A recently developed novel assessment approach, "Eating Sleeping Consoling" (ESC), prioritizes opioid withdrawal symptoms most functionally relevant for the newborn [43]. As opposed to a lengthy symptom checklist that includes potentially irrelevant physiologic symptoms, the functional ability to eat, sleep and be consoled are the primary measures for NAS severity and the parameters used to drive pharmacologic treatment. Institutional use of ESC resulted in a pharmacologic treatment rate of 12% in a cohort of newborns whereas 62% would have received medication with treatment decisions governed by FNAST [44]. For the subset of babies where a traditional FNAST protocol recommended pharmacologic treatment, the average FNAST score decreased by 0.9 points the following day without medication initiation. This decrease in withdrawal symptoms in the absence of pharmacotherapy suggests that babies who demonstrate moderate NAS symptoms may not require medication. Again, no data are available comparing how long-term outcomes might vary given different approaches to neonatal symptom control. Additionally, there is no known standard on an ideal proportion of opioid-exposed newborns that should be pharmacologically treated, nor is it known if neonatal morphine treatment is beneficial or harmful to the infant's neurologic development in the setting of NAS.

## 3. Pharmacologic care

Although the AAP recommends that non-pharmacologic care be the mainstay of treatment for NAS [4], most research has compared effectiveness of different medication regimens on NAS outcomes. Although recent studies suggest that buprenorphine [45,46] and methadone [47,48] may be more effective in reducing length of treatment (LOT) and LOS, when compared with morphine, the optimal pharmacological agent for NAS is yet to be determined [49,50]. Moreover, several studies suggest that standardization of care practices has more impact on short-term outcomes than does the specific medication utilized, as will be reviewed later.

## 4. Non-pharmacologic care

The impact of non-pharmacologic care on NAS is well recognized [4,36,51–54]. This is especially true for rooming-in and parental presence as they have been associated with significantly lower rates of pharmacologic treatment and shorter LOS [35,43,55–58], and may additionally promote mother-infant bonding and attachment when the mother is present.

### 4.1. Rooming-in

In 2007, Abrahams et al. published a seminal article on rooming-in for opioid-exposed newborns that demonstrated a LOS reduction from 23.5 days to 11.8 days when compared with traditional NICU care [55]. Since this time, additional studies have evaluated the impact of rooming-in on NAS outcomes with six studies recently assessed via a meta-analysis after meeting inclusion criteria in a systematic review of the literature [35,43,56,58–61]. No randomized control trials were available for inclusion. Four studies included retrospective cohorts with before- and after-assessments and two were QI reports. Pooled analysis of the six studies found rooming-in to be associated with lower proportions of pharmacological treatment (RR 0.33, 95% CI 0.18–0.63) and reduced LOS (weighted mean difference of −11.29 days, 95% CI 17.40–5.19) compared with standard NICU care. Given significant heterogeneity across studies, a sensitivity analysis was performed excluding three studies that involved multiple interventions or maternal group selection and still favored rooming-in for pharmacotherapy reduction (RR 0.20, 95% CI 0.17–0.47) and LOS (−14.12, 95% CI -19.28-8.97 days) [56]. The authors of the individual studies did not report increases in adverse events or readmissions.

In addition to a quiet, low stimulation environment, rooming-in facilitates privacy for mothers to provide skin-to-skin contact and breastfeeding. It also allows families greater access to their newborns to

provide additional non-pharmacologic care measures that decrease NAS symptoms, including holding, early response to hunger cues, and prompt calming when fussy. Despite benefits of rooming-in for opioid-exposed newborns, many hospitals do not or are unable to offer this model of care. A 2015 survey of 76 U.S. hospitals revealed that though most sites offer rooming-in with families during the initial observation period for NAS, a significant proportion (41%) never offer rooming-in and only 11% do so during pharmacologic treatment [17]. Other supportive care measures that promote maternal contact, including skin-to-skin contact, are reduced during pharmacologic treatment in these centers. Elements that do not utilize human contact increase when infants require pharmacotherapy, including the use of non-nutritive sucking and vibrating or moving seats/beds. It is important to note that newborn lack of human contact, especially with their mothers, may increase physiologic stress and be manifested in dysregulated behaviors. These behaviors may then be confused with opioid withdrawal or exacerbate NAS symptoms (disorganized feeding, difficulties sleeping, increased crying) and may potentially lead to increased pharmacologic treatment and LOS.

### 4.2. Parental presence

Investigators have attempted to determine how important continuous parental presence is to the benefits attributed to rooming-in. In a retrospective cohort study of 86 opioid-exposed mother-infant dyads cared for in a rooming-in setting, Howard et al. evaluated the impact of parental presence on hospital LOS, pharmacotherapy use, and mean FNAST score [57]. Maximum parental presence at the bedside for the entire newborn hospital stay was associated with a 9-day shorter LOS, and a 1-point decrease in mean daily FNAST score compared to infants with no parent present. Parental presence was higher and mean FNAST score lower for infants who breastfed. In multiple linear regression analysis, including adjusting for breastfeeding, parental presence remained significantly associated with a lower mean FNAST score of 0.8 points, 5.7 fewer days of opioid therapy, and a non-significant trend of shorter LOS of 5 days. Barriers to parental presence included lack of transportation, childcare responsibilities, off-site methadone dosing, residential substance disorder treatment requirements, intervention by child protection, and stigma and guilt experienced while watching infant withdrawal. Other studies of families of infants with NAS have also demonstrated similar themes [28,62].

As rooming-in and parental presence pose minimal risks, decreasing barriers to continuous rooming-in and implementation of interventions to increase parental presence are now evidence-based strategies to improve NAS care. In cases where child protective services have deemed that the newborn is unsafe to be discharged home with the biological mother, the infant can still benefit from care and presence of their mother within the safety of the hospital. If the newborn's mother is deemed unsafe to be with her infant within the hospital and/or if the mother herself disengages in care due to continued substance use or other mental health concerns, custodial arrangements should be made early in the newborn hospitalization. This allows designated kin or foster parents to be present to provide the necessary non-pharmacologic care and help promote attachment with one continuous care provider. Volunteer or staff cuddlers can also be utilized to help provide the benefit of human contact for non-pharmacologic care of NAS [35,36], and potentially infant mental health, when the biological mother or another designated “family member” is not available. The use of cuddlers, and of alternative kin or foster parents, is a largely unstudied area in the care of opioid-exposed infants both for short and long-term physical and mental health outcomes. The importance of attachment regarding infant mental health will be reviewed later in this article.

## 5. Models of care

### 5.1. Care models focused on standardized care and pharmacologic treatment

#### 5.1.1. Single center studies of care standardization

In an East Tennessee Children's Hospital NICU quality improvement (QI) project, standardized pharmacologic treatment protocols and FNAST use, family-centered communication, and a separate 16-bed specialized, rooming-in NAS unit yielded a 10.5 day reduction in LOS.[62]Although a noteworthy reduction, 40% of infants at this center were in the hospital for over 30 days and 6% for over 60 days. The University of Louisville NICU's implementation of a standardized, evidence-based treatment protocol of morphine every 3 h plus adjuvant clonidine was associated with reduced LOS from 42 days to 33 days when compared retrospectively with morphine every 4 h and adjuvant phenobarbital [64]. Although standardization of care using evidence-based treatment protocols was associated with significant improvements at both centers, LOS remained longer than the national mean of 23 days for pharmacologically treated infants. When considering these single center studies, it is important to note that other factors may contribute to longer LOS, including a greater proportion of mothers with active addiction and polysubstance use, and the type of opioid to which the infant was exposed (e.g., heroin vs long-acting MAT).

#### 5.1.2. Statewide collaboratives focused on care standardization

The Ohio Perinatal Quality Collaborative (OPQC) has engaged 52 of 54 Ohio NICUs in NAS QI. In a cohort study of 547 infants pharmacologically treated in 20 of these centers, those cared for in centers utilizing standardized weaning protocols had a significantly shorter LOS (22.7 days vs 32.1 days) independent of specific opioid used for treatment [16]. Initially, three of Ohio's six neonatology groups used wean-based treatment protocols and three did not. In a follow-up study, all six groups implemented a standardized weaning protocol, and retrospective analysis of 981 pharmacologically treated infants revealed significantly shorter LOS (23.7 days vs 31.6 days) in the three groups that previously lacked protocol-driven weaning guidelines, and sustained outcomes in the three groups using specific weaning guidelines at baseline [65].

In their recent quality report, the OPQC reported results of an 18-month intensive statewide initiative to improve care for pharmacologically treated infants with NAS [66]. Through their comprehensive multi-disciplinary QI initiative based on practices recommended in the Vermont Oxford Network (VON) Internet-based Newborn Improvement Collaborative for Quality (iNICQ) [67], the OPQC aimed to reduce duration of opioid treatment and hospital stay through 1) prenatal identification and counseling of women with OUD, 2) improved recognition and support of opioid-exposed women and newborns through trauma-informed, non-judgmental care, 3) high reliability standardized training of nurses in use of the FNAST, 4) adoption of a non-pharmacologic care bundle promoting maternal involvement, swaddling, skin-to-skin contact, a calm rooming-in environment, breastfeeding for mothers without active substance use or use of low-lactose formula if not breastfeeding, 5) a standardized pharmacologic treatment protocol, and 6) partnering with families for a plan of safe discharge. Of 3266 opioid-exposed infants cared for within 54 level 1, 2 and 3 nurseries, OPQC teams aimed for all infants to receive the non-pharmacologic care bundle, and to initiate pharmacologic treatment for 2 FNAST scores $\geq 9$. Using these criteria, 48% of babies were treated pharmacologically. Fifty six percent of hospitals chose a standardized morphine protocol, 35% chose a standardized methadone protocol, and 9% used other protocols. Regardless of the specific opioid replacement agent used, LOS significantly decreased across the collaborative from 18.3 days to 17.0 days. The final LOS achieved in this project was 6 days shorter than the national mean. Although reliable use of the non-pharmacologic care bundle improved over time, it was implemented

overall by only 58%. Total bundle compliance was lowered by less than recommended feeding practices, but compliance with swaddling, rooming-in and a calm environment was fairly reliable. Several factors were hypothesized to contribute to the issues with feeding, including limited evidence for efficacy of low lactose feedings when formula was used, and that half of mothers were not eligible to breastfeed due to illicit opioid use.

#### 5.1.3. National/international collaboratives

Vermont Oxford Network (VON) led a large-scale NAS QI collaborative between 2012 and 2015 [67]. A total of 199 centers participated and contributed data on 3458 infants. Most centers (98.5%) were from the U.S. with remaining centers from the United Kingdom and Canada. Interventions included developing and implementing standardized processes for the identification, evaluation, and treatment of infants with NAS, and measuring and reporting rates of NAS and drug exposure. Additionally, the effort promoted creation of a culture of compassion, understanding, and healing for the mother–infant dyad. Additional interventions included rooming-in, parental engagement in care, non-pharmacologic care as first-line treatment, breastfeeding for eligible mothers, standardized processes for safe discharge, and universal interdisciplinary NAS education. Among participating centers, the mean number of NAS guidelines increased from 3.7 to 5.1 of a possible 6 guidelines. Guideline implementation and adherence improved 1) maternal substance screening from 75.4% to 89.8%, 2) newborn evaluation and treatment from 76.2% to 95.0%, 3) standardized NAS scoring from 44.8% to 76.5%, 4) non-pharmacologic treatment strategies from 59.1% to 84.0%, 5) standardization of pharmacologic treatment from 68.0% to 91.6%, and 6) provision of human milk from 48.6% to 72.3%. A significant decrease was seen in the proportion of infants discharged on medication (e.g., phenobarbital) for NAS (from 39.7% to 26.5%). After adjusting for potential confounders, having a standardized NAS scoring process was associated with a 3.3 day shorter LOS. No LOS differences were demonstrated for the other interventions. The full cohort reduced LOS from 21 days to 19 days (P = .002) over 18 months. $170 million could be saved annually if these improvements were extended to all U.S. hospitals. LOS varied greatly across participating centers (14–33 days), highlighting significant persistent variation even during active promotion of standardization.

#### 5.1.4. NAS-dedicated treatment settings

Several studies have evaluated special units dedicated to care of opioid-exposed newborns. As previously reviewed, East Tennessee Children's Hospital developed a special NAS unit in which trained, dedicated staff provide care for opioid-exposed newborns, and parents can room in, within a calm, quiet developmentally appropriate environment. Study of the unit found a significant reduction in LOS of 10.35 days [63]. Although this reduction in LOS is significant, the final mean LOS (29.6 days) remained longer than the national mean and much longer than LOS achieved in other single-center QI studies that will be reviewed later in this article. Long-term impact of this dedicated unit was not evaluated.

Loudin et al. describe significant improvements in LOS when a special 15-bed neonatal therapeutic unit (NTU) with dedicated, trained nursing staff was developed in a tertiary care perinatal referral center in southern West Virginia in response to the vastly increased number of opioid-exposed newborns delivering in their region [68]. In contrast to the East Tennessee experience, this hospital was unable to allow parents to room-in with their infants due to space constraints. A related, free-standing NAS center, called 'Lily's Place', was subsequently developed. At Lily's Place, comprehensive care is provided through dedicated nurses, patient care assistant staff, NAS-trained volunteers, and social workers who assist in care coordination and safe transitions to home. Due to a limited number of patient rooms, Lily's Place is also unable able to allow parents to room-in. Although significant reductions in costs occurred with the new care sites, mean LOS for otherwise well, pharmacologically treated infants increased from 24 days in the NICU to 26 days in the NTU and 33 days in Lily's Place. As in other studies reviewed thus far, these LOS are longer than the national mean and considerably longer than in centers that promote rooming-in, parental presence, and other optimal non-pharmacologic care interventions. It is unknown how or if newborn LOS has bearing upon longer term outcomes in early childhood. It is also unknown how this type of care model may impact infant neurodevelopmental outcomes with the lack of a continuous caregiver to promote attachment.

#### 5.1.5. Home-based pharmacotherapy

In recent years, home-based pharmacotherapy has been trialed as a way to facilitate shorter LOS and promote maternal-infant bonding at home. Six retrospective studies on home-based pharmacotherapy [69–74] were recently analyzed in a systematic review of the literature after meeting inclusion and exclusion criteria [75]. This review demonstrated that outpatient weaning for select infants was associated with shorter LOS and reduced hospital costs compared with infants weaned in the hospital, with adverse events rarely reported. However, LOT was significantly longer in the outpatient weaning groups in the majority of studies including 32 days in one study [72] and 37 days in another [70]. A 2018 retrospective cohort study of infants enrolled in the Tennessee Medicaid program revealed that initial LOS was also significantly shorter for infants discharged home on medication (11 days vs 23 days) but LOT was more than 3 times longer compared with infants weaned prior to discharge to home (60 days vs 19 days; adjusted incidence rate ratio [aIRR] = 2.84) [77]. In this study, infants discharged on outpatient pharmacotherapy also had a 1.5 times increased risk of ED visits within 6 months of discharge compared with those weaned before discharge. Another recently published retrospective study of 774 infants cared for at the Royal Hospital for Women in Sydney, Australia demonstrated that outpatient pharmacologic care of opioid-exposed infants was sustainable and safe when infants were cared for in a coordinated multidisciplinary clinic with close follow-up and high parental compliance. However, similar to other studies of home-based pharmacotherapy, LOT was significantly prolonged and even more so in this center with a median LOT of 76 days (range 35–120 days) [76]. While home-based pharmacotherapy models of care appear effective in decreasing time spent in the hospital with subsequent reductions in medical costs, and may help aid maternal-infant bonding with earlier transitions to home, little remains known about the long-term impact of prolonged opioid exposure on an infant's neurodevelopment or future risk for addiction. Given animal data that demonstrates potential negative effects [78,79], it may be better to focus on initiatives that aim to decrease postnatal opioid exposure through optimized non-pharmacologic care and medication treatment decisions tailored to symptoms that are most impacting an infant's function rather than on those aimed only to decrease LOS. If home-based pharmacotherapy is to be implemented, more frequent weaning than that performed in studies to date should be considered to help limit postnatal opioid exposure. Additionally, close coordinated follow-up with neurodevelopmental assessments, and reporting on these outcomes in the literature, is encouraged.

### 5.2. Care models focused on non-pharmacologic care and symptom prioritization

Several recent single center QI studies have demonstrated the impact of baby-centered NAS care bundles, wherein parents serve as the newborn's primary caregiver, non-pharmacologic care is optimized in a private room, and providers prioritize symptoms most relevant to an infant's physiologic function. In such models, pharmacologic treatment is deferred until these measures have proved insufficient to treat the infant's opioid withdrawal symptoms, unless significantly concerning symptoms are present that prompt earlier treatment [35,36,43].

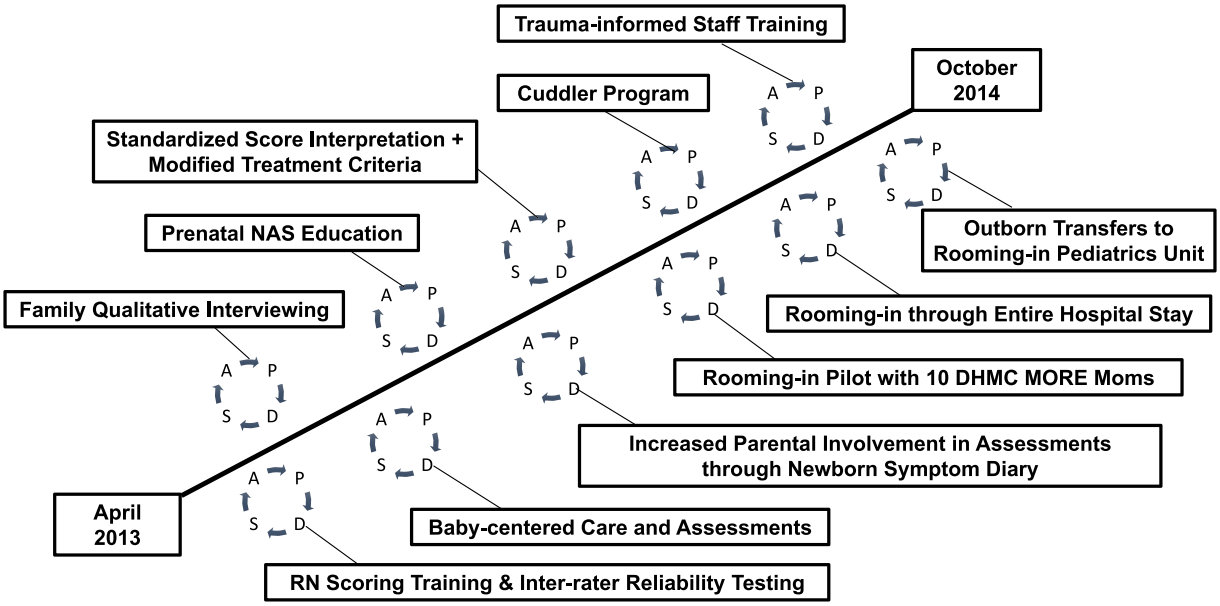


**Fig. 1.** CHaD's 18-month NAS QI improvement project.

*5.2.1. Children's Hospital at Dartmouth-Hitchcock*

In a formal QI initiative, launched as part of the 3-year VON NAS iNICQ, the Children's Hospital at Dartmouth-Hitchcock (CHaD) transformed their care of opioid-exposed newborns and demonstrated improved short-term outcomes and cost savings [35]. Over an 18-month period involving 163 opioid-exposed infants and more than 10 PDSA cycles (Fig. 1), CHaD changed its care model from one focused on initiating pharmacologic treatment in the NICU, based on FNAST criteria, to one focused on parents providing non-pharmacologic care in private rooms throughout the entire hospitalization and a family-centered approach to functional symptom assessment. A subset of mothers was educated prenatally regarding ways they could best prepare for their baby's birth hospitalization, such as planning to stay with their baby in a private room throughout the entire hospital stay, providing frequent skin-to-skin contact, breastfeeding, and planning in-hospital family and friend support while limiting excessive visitors to avoid disrupting the infant. Education also included planning for safe transitions to home, including early follow-up with the newborn's medical provider, a home visiting nurse, and strategies for withdrawal symptoms such as difficulty consoling. Rather than reflexively starting babies on pharmacologic treatment for 3 FNAST scores $\geq 8$ (or $2 \geq 12$), providers prioritized symptoms of poor feeding, difficulties sleeping, inconsolability, tachypnea, fever, vomiting, or diarrhea over other symptoms that were present but not functionally impacting the newborn (increased tone, tremors, sneezing, yawning) prior to considering pharmacologic treatment. A volunteer cuddler program was implemented to assist during times when parents needed to be away. Utilizing baby-centered assessments performed around the baby's natural sleep-wake-feeding cycle, staff trained and reliable in FNAST scoring, parents providing optimal non-pharmacologic care in their own room, and Finnegan symptom prioritization, CHaD significantly decreased the proportion of morphine treatment from 46% to 27%, use of adjunctive agents from 13% to 2%, LOS from 16.9 days to 12.3 days, and mean hospital costs from $19,737 to $8,755 per pharmacologically treated infant. Costs for the population of opioid-exposed infants, which included close to 10% of all births by the end of the study period, fell from $11,000 to $5,300. There were no adverse events. Most mothers were receiving MAT and many received comprehensive care in an addiction treatment program affiliated with the hospital [35].

*5.2.2. Yale New Haven Children's Hospital*

In a 6-year QI initiative involving 287 methadone-exposed newborns, Grossman et al. demonstrated that a coordinated multi-disciplinary NAS program empowering parents to be their baby's primary caregiver and moving care from the NICU to a rooming-in environment with non-pharmacologic care optimized yielded short-term NAS improvements without increased adverse outcomes [43]. Yale implemented eight interventions over their project's duration: 1) standardization of non-pharmacologic care with rooming-in and optimal feeding practices; 2) transfer of infants requiring increased observation or pharmacologic treatment from the well-baby nursery to the inpatient pediatrics unit rather than to the NICU; 3) development and implementation of the ESC approach to assessment and medical decision making; 4) spread of change concepts to the NICU for infants requiring care there for any reason; 5) change from a gradual to rapid weaning of morphine for those requiring pharmacologic treatment; 6) prenatal parent education; 7) morphine given on an as needed, rather than scheduled, basis; and 8) empowering messaging for parents stressing that parental presence is the primary medical treatment for NAS. Yale decreased pharmacologic treatment from 98% to 14%, LOS from 22.4 days to 5.9 days, and hospital costs from $44,824 to $10,289 per treated infant with their QI initiatives. Rates of breastfeeding increased from 20% to 45% [43].

*5.2.3. Boston Medical Center*

In another comprehensive QI initiative, the Boston Medical Center (BMC) aimed to improve NAS inpatient outcomes through 1) adoption of a non-pharmacologic care bundle (similar to that implemented at the Children's Hospital at Dartmouth-Hitchcock and Yale-New Haven Children's Hospital), 2) empowering prenatal/parental messaging regarding the importance of parental presence at the bedside and of the mother being her newborn's primary NAS treatment, 3) Finnegan symptom prioritization with pharmacologic treatment initiated only if an infant had difficulties feeding, excessive vomiting, diarrhea, poor consolability, and/or sleep not responsive to optimization of non-pharmacologic care as per the CHaD model, 4) staff QI project education, 5) a switch from morphine to methadone as the primary opioid for infants requiring pharmacologic treatment, 6) incorporation of a cuddler program to assist in caring for opioid-exposed newborns, and 7)

function-based ESC assessments and pharmacologic treatment decisions using a novel ESC-based nursing flowsheet [36]. The BMC program yielded significant reductions in LOS (17.4 days vs 11.3 days), proportion of infants requiring medications for NAS (87.1% vs 40.0%), adjunctive agent use (33.6% vs 2.4%), opioid treatment days (16.2 days vs 12.7 days), and total hospital charges ($31,825 vs $20,668 per infant). Parental presence also significantly increased from 55.6% to 75.8%. Percent of infants pharmacologically treated decreased significantly following implementation of the non-pharmacologic care bundle, symptom prioritization, and parental and staff QI education. Later PDSA cycles of methadone treatment, the ESC nursing flowsheet and the cuddler program were not associated with further reductions in LOS or proportion of infants pharmacologically treated [36].

Although these three single center QI initiatives, promoting rooming-in, parental presence, baby-centered non-pharmacologic care and symptom prioritization, have achieved significantly lower rates of pharmacologic treatment and shorter LOS than initiatives focused on standardized care and pharmacologic weaning protocols, their impact on long-term neurodevelopmental outcomes is not yet understood. It is also important to note that for each program, a high proportion of mothers were established in recovery and on long-acting MAT with a lower proportion of active illicit substance use which may differ from other single-center studies reviewed in this article. Additionally, these studies focused on biological mother-infant dyads and did not explore clinical scenarios where infants were cared for by an alternate caregiver (e.g., foster mother). This is a largely uninvestigated context across all studies.

### *5.3. Care models focused on comprehensive treatment for pregnant women and their newborns*

Although much attention has been paid to higher rates of NAS and associated inpatient healthcare expenditures related to perinatal opioid exposure, there has been less attention given to the increased risk of prematurity, low birth weight, placental abruption, and stillbirth associated with untreated prenatal OUD [80,81]. There are better maternal and child outcomes when pregnant women with OUD receive MAT [82], especially when it is provided within multi-disciplinary programs that include obstetrical, mental health, and substance use disorder treatment [83]. Benefits of these integrated models include increased prenatal care attendance, and decreased rates of illicit substance use, placental abruption, fetal loss, preterm labor, prematurity, and fetal growth restriction [80,84–86].

Although some studies demonstrate similar reductions in preterm delivery and low birth weight for groups of pregnant women treated with buprenorphine or methadone [81], others find buprenorphine superior [32]. In a systematic review and meta-analysis of prenatal buprenorphine as compared to methadone, Brogly et al. found that the unadjusted NAS treatment risk was lower (RR 0.90) and mean hospital LOS shorter (−7.23 days) for infants prenatally exposed to buprenorphine [87]. A significantly shorter treatment duration (−8.46 days) and lower cumulative morphine dose (−3.60 mg) was also seen for buprenorphine-exposed infants. MAT with buprenorphine was also favored regarding gestational age, birth weight, body length, and head circumference. No difference was demonstrated between treatment agents for risk of delivery < 37 weeks.

Because methadone may be a more efficacious MAT agent in some pregnant women due to its lower rate of discontinuation [32,82,87], the choice of MAT should not be based solely on anticipated neonatal outcomes but instead should be individualized to decrease maternal risk of OUD relapse during pregnancy. The risk for discontinuation of either type of MAT and relapse exists for all pregnant women with OUD and merits close monitoring and continued support in a comprehensive treatment program before and after delivery [88]. In a recent Massachusetts study of 4154 deliveries to women with OUD, Schiff et al. reported 242 maternal overdoses (231 nonfatal, 11 fatal) in the year before and after delivery. The highest overdose rate occurred 7–12 months after delivery, and the lowest rates were observed in women receiving MAT during the early postpartum period [89]. Safe transitions to home are important not only for the infant, but also for the mother.

Optimal infant outcomes also depend on a mother's sustained recovery and her mental health. Mood disorders, anxiety, and PTSD are common comorbidities of OUD in women. Untreated maternal mental health conditions are independently associated with increased preterm birth [90] and decreased maternal-infant attachment [91]. Treatment is critical to optimizing neurodevelopmental outcomes for infants as untreated perinatal mood disorders have been associated with poor neurodevelopmental outcomes [92]. As such, pregnant women with OUD benefit from comprehensive mental health treatment including counseling and medication. In the absence of medication intolerance or other psychiatric complications such as bipolar affective disorder, Selective Serotonin Reuptake Inhibitors (SSRIs) are first line therapeutic agents for anxiety, depression, and PTSD for pregnant women. Although concern exists regarding SSRIs increasing NAS symptoms and rates of pharmacologic treatment [93–96], optimal maternal mental health is of higher priority in order to promote attachment and optimize the mother's ability to care for her infant. If pharmacotherapy is required for NAS, safe medication options are available and non-pharmacologic care can still serve as first-line treatment for medicated infants.

An additional benefit to caring for women with substance use disorders in a comprehensive treatment program is that more attention is paid to the mother's other substances of misuse or dependency. These additional exposures have been linked to increased withdrawal severity in the newborn [97]. One of the most frequent co-exposures is maternal tobacco use with a reported 88–95% of women with OUD also smoking cigarettes [98]. Cigarette smoking in pregnancy has been linked to greater severity in NAS symptoms [95], likely due to the increased stress and abstinence signs exhibited by neonates following in-utero nicotine exposure [99]. Studies have also demonstrated an increased need for pharmacotherapy [100], higher doses of morphine needed [101], longer treatment duration [101,102] and longer LOS [101] in newborns with opioid and tobacco co-exposure. Importantly, prenatal tobacco use also increases risks for prematurity, growth restriction and low birth weight [100,103] and Sudden Infant Death Syndrome (SIDS) [104]. Although data are limited, prenatal smoking cessation and harm reduction interventions can be effective in improving maternal and newborn health and should be strongly encouraged [98]. Continued smoking cessation and passive smoke avoidance education are also essential in decreasing the infant's risk for respiratory tract infections, asthma, and SIDS.

#### *5.3.1. Integrated models of care for the mother-baby dyad*

*5.3.1.1. University of North Carolina's Horizons program.* Founded in 1993, Horizons is the archetype for comprehensive care for mother-infant dyads with SUD [105]. It includes prescription of MAT, provision of mental health care, peer support, and prenatal education focused on intrapartum pain management and in-hospital neonatal care. Horizons facilitates multi-disciplinary, mother-baby centered care of opioid-exposed newborns through trauma-informed, non-pharmacologic care during the newborn hospitalization. Horizons' levels of care and extensive community integration are particularly noteworthy. Varied intensities of maternal OUD treatment are available and individualized to the pregnant woman, from outpatient MAT to residential care where a mother can live with her children while undergoing inpatient treatment. Community reintegration services are particularly robust, including legal services, job training and placement services, and substance-free transitional housing.

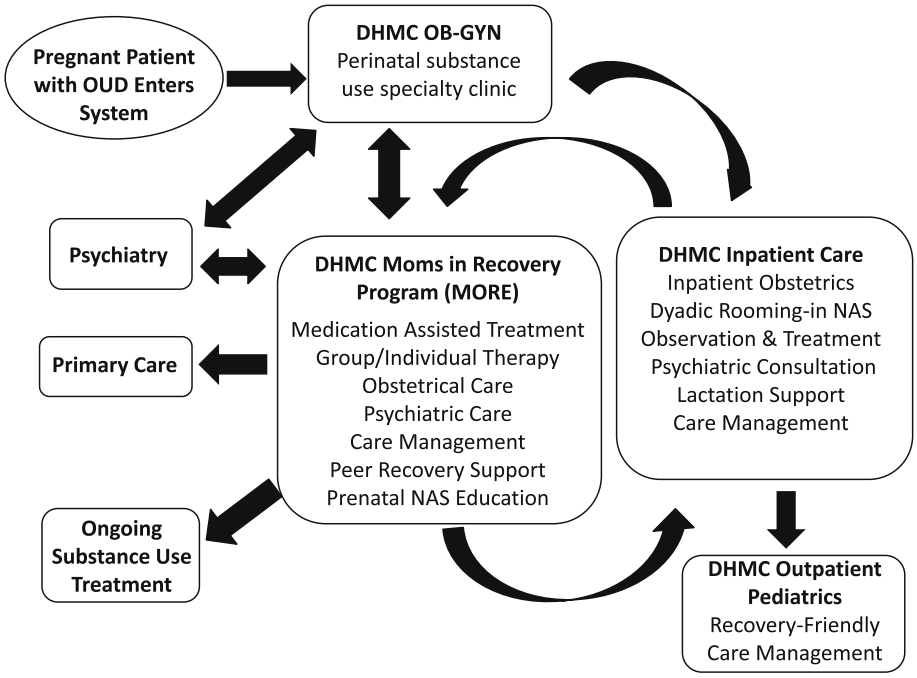


**Fig. 2.** DHMC's Moms in Recovery (MORE): Integrated care for women and infants with perinatal opioid exposure.

*5.3.1.2. Dartmouth-Hitchcock Moms in Recovery program.* Dartmouth-Hitchcock (D-H) Moms in Recovery (MORE) was established in 2013 as a comprehensive, multi-disciplinary prenatal care service for women with OUD and co-occurring psychiatric conditions [106,107]. When a woman discloses an OUD anywhere in the D-H health system (which cares for about half of the region's population), she is referred to the MORE program. MORE has cared for more than 160 pregnant and parenting women since its inception (D Goodman, personal communication, 2019). An addiction psychiatrist provides MAT and comprehensive substance abuse and psychiatric care. Licensed social workers, a licensed drug and alcohol counselor, and behavioral health specialists provide group counseling sessions and support services. A certified peer recovery coach provides lived-experience support to women in the program. A midwife provides prenatal and postpartum care including family planning and primary reproductive health services. A team of pediatricians delivers prenatal education sessions on NAS and on-site dyadic well-child care for newborns and siblings. Social workers and the recovery coach coordinate referrals to community services regarding intimate partner violence, early intervention, and subsidized housing. As not all pregnant women with substance use disorders participate in the MORE program, D-H also has a dedicated SUD prenatal clinic for women who receive addiction treatment at other programs, and a related recovery-friendly pediatric practice (Fig. 2). These care models have been associated with increased numbers of prenatal visits, adequate prenatal weight gain, adherence to substance disorder treatment, and decreased rates of non-prescribed opioid use, low birthweight, prematurity, pharmacotherapy for NAS, and increased postpartum retention in MAT (Frew JR, Goodman DJ, Saunders EC. Manuscript in preparation. 2019).

*5.3.2. Safe transitions to home and post-discharge care of the opioid-exposed infant*

Most studies to date regarding opioid-exposed infants have focused on in-hospital care while little has been published on safe transitions to home and post-discharge care of the opioid-exposed newborn especially when care is provided outside of comprehensive, coordinated care settings. The importance of developing a “Plan of Safe Care” for substance-exposed infants has been highlighted and now mandated in the U.S. through the 2016 Comprehensive Addiction and Recovery Act, commonly referred to as CARA [132]. CARA requires that a Plan of Safe Care address the health and substance use disorder treatment needs of the infant and affected family or caregiver. The Substance Abuse and Mental Health Services Association (SAMHSA) has recently published “Clinical Guidance for Treating Pregnant and Parenting Women with Opioid Use Disorder and their Infants” in which recommendations, web-based resources, and discharge checklists can be found to help providers develop Plans of Safe Care for opioid-exposed mother-infant dyads [133]. Safe discharge planning optimally starts prenatally with referrals to community agencies (e.g., home visiting programs and parenting resource centers) and helps ensure that the home is safe and equipped for care of a newborn. As noted previously, Plans of Safe Care should include continued maternal opioid use disorder treatment, especially in the high risk postpartum period. Caregiver abstinence from any substance use in parenting should be strongly encouraged, not only for the mother but also any other infant caregiver. Parenting education should include ways to identify signs of early hunger and how to optimize feeding including if the baby has any difficulties after discharge. Parenting education should include instruction on ways to calm a fussy baby and the importance of never shaking a baby. Parents should be educated on safe sleep practices including safe swaddling and the importance of no co-sleeping, as well as the importance of early follow up with the baby's primary care provider (PCP) for routine well-baby care and any difficulties with feeding, sleeping, consoling, or other acute signs of increased NAS or illness. Post-discharge follow-up with the baby's PCP and home visiting nurse agency, and referral to early intervention services, should be made before hospital discharge. Newborn follow-up evaluations should include assessment of the baby's and family's transition to home, infant feeding, elimination and weight patterns, and any signs of increased opioid withdrawal. Support and encouragement for continued breastfeeding can be provided by the PCP, home visiting nurse, and/or through referral to a lactation consultant or other community breastfeeding support agency. PCPs can further reinforce referrals, made prenatally and in the birth hospital, to services that provide perinatal and infant health care to promote optimal physical and emotional health of the mother-infant dyad and reduce the risk of infant or maternal morbidity and mortality [133], especially as related to parenting resource centers, home visiting nurse

programs, early intervention, and other social supports needed by the family including help with transportation, housing, and food security.

## 6. Developing an optimal model of care for opioid-exposed newborns and their families

### 6.1. Impact of care models on maternal-infant attachment and infant mental health

As mentioned previously, little is known about how family-centered care models, or rooming-in postnatal care, might impact longer-term developmental outcomes for children who had NAS as newborns. There is extensive literature on how early maternal-infant attachment affects long-term outcomes, and this is worth reviewing in this context.

In a prospective cohort study of 31 newly delivered young, unmarried, first time mother-baby dyads, study authors compared care provided in one hospital that promoted skin-to-skin contact and rooming-in with one that limited contact to every 4 h for feedings [108]. The 15 mothers in the rooming-in group demonstrated significantly more time looking at and talking to their infants and less time watching television or talking with others. Mothers in the rooming-in group also spent significantly more time touching their infants in age-appropriate manners and had higher ratings on the attentiveness and touching subscales than did the 16 mothers in the limited contact group. Although this study is not specific to care of opioid-exposed newborns, it is important that we consider the impact of rooming-in on mothering behaviors (e.g., looking at and talking to infant, touching infant in an age-appropriate manner) and how these behaviors may aid in providing calm, non-stimulating, supportive and developmentally-appropriate care for newborns at risk for problematic withdrawal symptoms. More importantly, these behaviors may aid in improving the mother-infant attachment relationship. Protecting and promoting infant neurologic development and mental health is an important aspect of care that has been insufficiently considered in the literature and clinical practice regarding NAS to date.

The formal study of infant mental health is a multidisciplinary research and clinical practice 'enterprise' [109]. It is based on the understanding that the postnatal period is a time of rapid neurological development [110] and it recognizes that infant brain development is experientially- and environmentally-dependent [111]. For an infant, experience and environment are relationally-based, making attachment fundamental for infant mental health. Loosely defined, attachment refers to an affective relationship with a particular, preferred individual, usually the person providing consistent care for the infant [109]. This generally occurs in the context of the infant's primary attachment relationship, most often with his/her biological mother [112]. Infants who experience deficient or absent primary attachment relationships are known to experience significant long-term behavioral, psychological and emotional difficulties [113]. Mothers with untreated SUD may have difficulty with attachment when their active addiction consumes much of their energy and attention.

Newborn birth hospitalization can disrupt attachment between the infant and primary caregiver(s) in the first few days of life [114]. Prolonged hospitalizations for NAS are likely to further contribute to disruptions in attachment, especially when care is provided in the NICU where the ability to room in is typically limited [17,19]. and where mothers may spend less time with newborns due to feeling unwelcomed or judged by hospital staff [28,29].

Attachment is largely dependent on three key elements: proximity, reciprocity and commitment [115]. Proximity includes touching and eye contact, which enable the caregiver to communicate with the infant. Reciprocity involves interaction between the infant and the caregiver, including how well the caregiver responds to the cues the infant sends. Commitment describes the ongoing nature of the relationship. The highly technological environment of most NICUs is often not conducive to these key attachment elements [114]. The NICU can be especially restrictive when an infant has an acute medical condition that may include intubation, intensive cardiorespiratory monitoring, and incubator warming – all of which may further restrict maternal-infant contact.

For these reasons, providing care to opioid-exposed newborns in a calm private room with their own mother or another consistent, attentive caregiver should be prioritized. When this is not possible given an individual hospital setting, it is especially important for nurses to understand their role in supporting and facilitating mother-infant attachment [116]. Interventions and strategies that can help facilitate attachment in the technological intensive care environment include: skin-to-skin care [117], breastfeeding [118], participation in routine care (e.g., feeding, bathing, diaper changes) [119], and psychosocial support of the mother [120]. All of these interventions have proven beneficial to the development of healthy attachment in NICU environments. It is also important for staff to provide care in a trauma-informed manner, as many women with SUD have a history of physical and/or sexual trauma and can be re-traumatized by interactions with health care providers [121]. We refer the reader to two excellent reviews on trauma-informed care in the NICU for the support of women with SUD and implications for early childhood development [121,122].

A recent extensive systematic review failed to identify any interventions intentionally aimed at optimizing infant mental health for hospitalized opioid-exposed infants (S Blythe, personal communication, 2018). In response to this gap in the literature, investigators qualitatively studied how nurses promote attachment for hospitalized newborns experiencing NAS [123]. Nurses implement a range of activities to promote attachment, but articulate difficulties in promoting attachment for infants with NAS when the mother is absent [124]. In other studies, mothers have shared barriers to being present including lack of transportation, childcare responsibilities, need to leave the hospital to receive their MAT, residential SUD treatment program requirements, feeling judged, stigma and guilt [28,29,36]. Maternal absence may also stem from physical or mental health difficulties, active substance use issues, and/or the involvement of child protective services [125]. As such, hospitals and providers can assist mothers to overcome these barriers through care coordination, substance use and mental health disorder treatment, and trauma-informed care.

#### 6.1.1. Interventions to improve infant attachment

Although advocacy for the presence of the biological mother in the care of the opioid-exposed infant has recently increased, the focus has been on improving short-term neonatal outcomes related to pharmacotherapy and LOS [35,36,43,56,58,126,127]. In these studies, attachment is not acknowledged from the point of healthy neurological development or the promotion of the infant's mental health, but rather as a physical symptom reliever. One recent exception is a mixed methods study on skin-to-skin contact in opioid-dependent mother-infant dyads, in which investigators quantitatively measured pre- and post-intervention salivary cortisol levels, heart rates, attachment scores and "dyad synchronization" following a brief educational intervention on the benefits of skin-to-skin contact [128]. Currently, the research team is collecting data from maternal interviews, and data on infant LOS and hospital costs. There is a clear need to consider the infant's mental health and development in these contexts of care [129].

### 6.2. Key components of optimal care for opioid-exposed newborns

The executive summary of a joint workshop of the National Institute of Child Health and Human Development, American College of Obstetricians and Gynecologists, American Academy of Pediatrics, Society for Maternal-Fetal Medicine, Centers for Disease Control and Prevention, and the March of Dimes, states that care of the opioid-exposed infant should focus on four goals: 1) support of vital neonatal functions and development, 2) initiation and support of family bonding, 3) prevention of complications, and 4) family education and provision

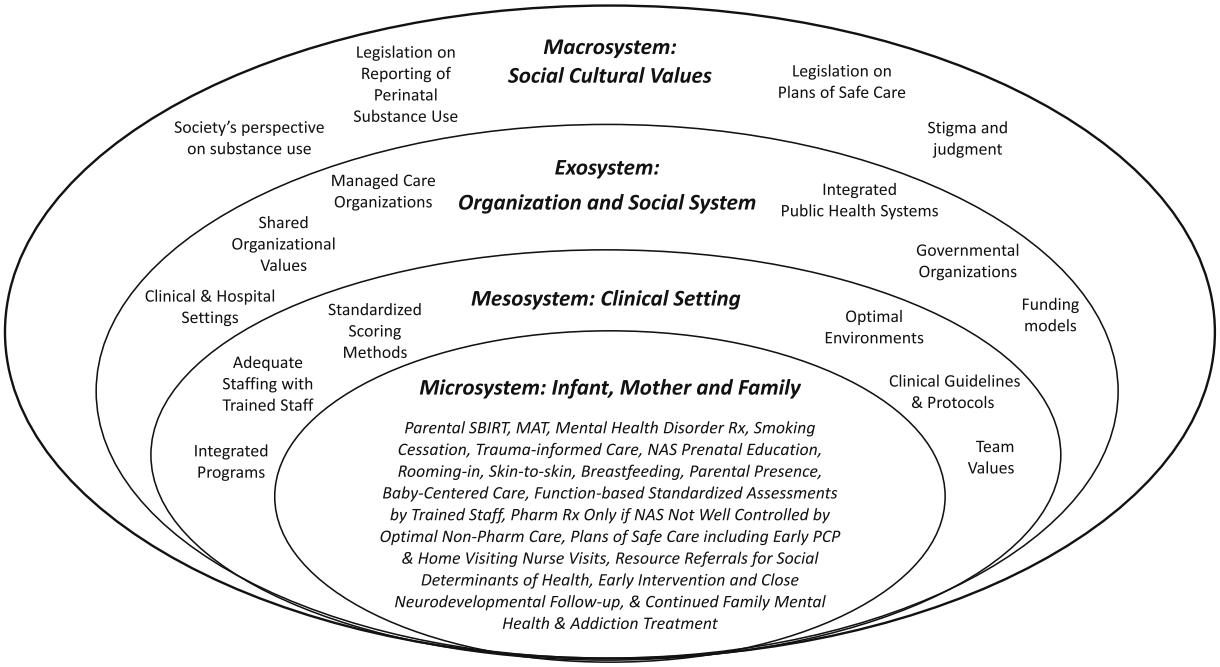


**Fig. 3.** Social ecological approach to NAS care.

**Table 1**
Key components of an optimal model of care for opioid-exposed newborns.

- Prenatal Screening, Brief Intervention, and Referral to Treatment (SBIRT) for pregnant women with substance use disorders
- Maternal comprehensive, multi-disciplinary, individualized addiction treatment including buprenorphine as preferred MAT when appropriate, behavioral and mental health counseling, and medication treatment for maternal co-occurring psychiatric conditions
- Prenatal education for families on NAS and ways they can optimize fetal and neonatal outcomes through prenatal care, smoking cessation, rooming-in, parental presence, and non-pharmacologic care
- Trauma-informed, non-judgmental care individualized to the neonate, mother, and family
- Rooming-in in a calm, nurturing environment that promotes parents as the newborn's primary care providers, and ensures adequate rest and support for the infant and parents
- Frequent skin-to-skin contact with an alert, rested caregiver
- Feeding on demand at early hunger cues and until content
- Breastfeeding and/or provision of mother's milk (unless medically contraindicated)
- Use of pacifiers for non-nutritive sucking only after an infant is well-fed
- Staff trained and competent in performing consistent NAS neurobehavioral assessments
- Assessments performed after feedings while the infant is held by a parent/caregiver
- Non-pharmacologic care interventions (e.g., rooming-in, parental presence, skin-to-skin, holding, swaddling, calm environment, limiting visitors, non-nutritive sucking) optimized to their fullest extent possible and individualized to the clinical setting prior to considering pharmacologic treatment
- Treatment decisions prioritized to symptoms physiologically and neurobehaviorally relevant to the infant's function and gestational age
- Pharmacologic treatment initiation, escalation, and weaning performed using a standardized protocol
- Development of a Plan of Safe Care for the mother-infant dyad that includes referrals to community support agencies (including home health visiting programs and parenting centers), substance use disorder treatment for the family (including smoking cessation interventions), and early and frequent follow-up with recovery-friendly primary care, obstetric, and addiction treatment providers
- Referrals to early intervention services and careful follow-up for optimal neurodevelopment

of adequate medical and social resources after discharge [130]. When considering these treatment goals and an optimal care model for opioid-exposed newborns, we should think comprehensively about care that includes the mother and family, and considers the newborn's individual clinical context, the greater health care system, and society as a whole. In a recent article that proposes a social ecological approach, comprehensive care models for the opioid-exposed infant can be designed to address the 1) *micro-system* (infant, mother, and family), 2) *meso-system* (standardized evidence-based care guidelines, rooming-in, trauma-informed care), 3) *exo-system* (hospitals, medical insurance programs, public health systems), and 4) *macro-system* (governmental policies related to safe transitions to home and availability of comprehensive treatment for OUD, educating the community on the science of addiction and decreasing stigma) [131]. We refer the reader to Fig. 3 and Table 1 for key components of optimal care models for opioid-exposed newborns that include their mothers and families.

## 7. Conclusions

Models of care for NAS that promote baby-centered, function-based, non-pharmacologic care, with the mother as the primary means of treatment, may be more effective in reducing LOT and LOS than those focused on specific medications, protocol standardization, or home-based pharmacotherapy. Given the evidence to date, care for opioid-exposed newborns should occur in settings that maximize rooming-in and trauma-informed supportive care for families. Social ecological approaches to care should be incorporated to help optimize maternal-infant health outcomes and safe transitions to home. Further studies are needed to assess these models of care on maternal-infant attachment and long-term neurodevelopmental outcomes. Research investigating scenarios where the infant has been separated from the mother (e.g., foster care) are also warranted as care models used in these situations will likely differ.

### 7.1. Practice points

- Different FNAST score thresholds affect the likelihood an infant will be prescribed medication
- Standardized treatment protocols reduce LOS regardless of specific medication used
- Care provided in NAS-dedicated settings is associated with varied impacts on LOS
- Care models focused on symptom prioritization and non-pharmacologic care are associated with lower rates of pharmacotherapy, LOS, and hospital costs compared with score-based, standardized treatment including that provided in dedicated NAS treatment settings
- Home-based pharmacotherapy significantly reduces LOS but significantly increases LOT and may increase post-newborn discharge ED visits
- Better health outcomes are experienced by dyads cared for in comprehensive, multi-disciplinary treatment programs

### 7.2. Research directions

Role of the following on short- and long-term NAS outcomes including proportion of infants pharmacologically treated, LOS, hospital costs, maternal-infant attachment, childhood neurodevelopment, and future risk of addiction:

- FNAST score vs ESC function-based assessments and medication treatment decisions
- Specific medication used when non-pharmacologic care is optimized prior to pharmacotherapy initiation
- Cumulative postnatal opioid exposure among infants weaned in vs out of hospital
- Rooming-in care models using biological parents vs foster parents (or designated kin) vs hospital cuddlers
- Protecting and promoting infant mental health during withdrawal and hospitalization in varied care settings

## Authors' contributions to manuscript

Dr. Whalen led conception and design of the review, drafted all sections except that by Dr. Blythe, critically reviewed and incorporated revisions provided by co-authors, and finalized the version submitted.

Dr. Holmes critically reviewed and revised the review, and provided final approval of the version submitted.

Dr. Blythe co-led conception of the review, wrote the section on infant mental health and attachment, critically reviewed and revised the review providing additional items for inclusion, and provided final approval of the version submitted.

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