

# Phenobarbital and Clonidine as Secondary Medications for Neonatal Opioid Withdrawal Syndrome

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abstract

**BACKGROUND AND OBJECTIVES:** Despite the neonatal opioid withdrawal syndrome (NOWS) epidemic in the United States, evidence is limited for pharmacologic management when first-line opioid medications fail to control symptoms. The objective with this study was to evaluate outcomes of infants receiving secondary therapy with phenobarbital compared with clonidine, in combination with morphine, for the treatment of NOWS.

**METHODS:** We performed a retrospective cohort study of infants with NOWS from 30 hospitals. The primary outcome measures were the length of hospital stay, duration of opioid treatment, and peak morphine dose. Outcomes were compared by group by using analysis of variance and multivariable linear regression controlling for relevant confounders.

**RESULTS:** Of 563 infants with NOWS treated with morphine, 32% ( $n = 180$ ) also received a secondary medication. Seventy-two received phenobarbital and 108 received clonidine. After adjustment for covariates, length of hospital stay was 10 days shorter, and, in some models, duration of morphine treatment was 7.5 days shorter in infants receiving phenobarbital compared with those receiving clonidine, with no difference in peak morphine dose. Infants were more likely to be discharged from the hospital on phenobarbital than clonidine (78% vs 29%,  $P < .0001$ ).

**CONCLUSIONS:** Among infants with NOWS receiving morphine and secondary therapy, those treated with phenobarbital had shorter length of hospital stay and shorter morphine treatment duration than clonidine-treated infants but were discharged from the hospital more often on secondary medication. Further investigation is warranted to determine if the benefits of shorter hospital stay and shorter duration of morphine therapy justify the possible neurodevelopmental consequences of phenobarbital use in infants with NOWS.



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**WHAT'S KNOWN ON THIS SUBJECT:** Phenobarbital and clonidine are the most-commonly used secondary medications for the treatment of neonatal opioid withdrawal syndrome. Variation between centers exists, and few studies directly compare the 2 medications in neonatal opioid withdrawal syndrome treatment.

**WHAT THIS STUDY ADDS:** In this multicenter retrospective cohort study of 180 infants, we found that phenobarbital-treated infants had shorter length of stay and, potentially, fewer days of morphine treatment than clonidine-treated infants but were sent home on medication more often.

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Because of the ongoing opioid epidemic, >32 000 opioid-exposed infants are now born annually in the United States,<sup>1</sup> with the majority showing at least some signs of neonatal opioid withdrawal syndrome (NOWS).<sup>2</sup> Many knowledge gaps remain regarding optimal treatment of infants with NOWS. It is generally accepted that nonpharmacologic treatment (swaddling, low-stimulus environment, rooming in, skin-to-skin) should be the first-line therapy, with opioid medication added if this approach fails to adequately control symptoms.<sup>3</sup> When opioid therapy is not sufficient, secondary medications must be considered. There is wide variation among institutions with respect to selection and initiation of secondary medication.<sup>4,5</sup> Across the country, selection of a secondary medication for NOWS has largely been based on local preference and protocol, possibly dictated by concern for potential side effects.

Phenobarbital and clonidine are the most commonly used secondary medications for NOWS.<sup>6</sup> Phenobarbital is a barbiturate and potent sedative. Commercially available phenobarbital formulations contain 13.5% alcohol in the solution and 15% alcohol in the elixir, although compounded alcohol-free solutions are available.<sup>7</sup> Clonidine decreases noradrenergic activity and lessens symptoms of withdrawal, such as tachypnea, tachycardia, fever, sweating, sneezing, and yawning.<sup>8</sup> Clonidine solution is not commercially available so it must be compounded, which increases risk of dosing errors.<sup>9</sup> Few safety, pharmacokinetic, and pharmacodynamic data are available for clonidine,<sup>10</sup> and although data exist in these areas for phenobarbital,<sup>11</sup> studies comparing the 2 as a treatment of NOWS are lacking. Only 2 small studies of 68 patients<sup>12</sup> and 25 patients<sup>13</sup> have prospectively compared the effects of phenobarbital and clonidine in infants

treated with morphine for NOWS. In both of these studies, infants treated with phenobarbital had significantly shorter morphine treatment days and shorter hospital length of stay. This is despite researchers in the first study having used morphine plus phenobarbital (M + P) or morphine plus clonidine (M + C) as initial treatment and those in the second study having used phenobarbital or clonidine as adjunctive therapy after failure of morphine. However, in both studies, phenobarbital was continued as an outpatient, whereas clonidine was weaned and discontinued before discharge, leading to an overall longer length of treatment of infants given phenobarbital. In contrast, researchers in a single retrospective study comparing different NOWS treatment protocols found that if a secondary medication was needed, using morphine every 3 hours with clonidine was associated with a shorter length of hospitalization and duration of morphine treatment than using morphine every 4 hours with phenobarbital.<sup>14</sup>

Given the paucity of literature on this topic with conflicting findings, additional studies are needed to compare clonidine and phenobarbital as secondary NOWS agents. The objective with this investigation was to compare the in-hospital outcomes of length of morphine treatment, length of hospital stay, and peak morphine dose in infants treated with M + P versus infants treated with M + C as part of a large multicenter observational study evaluating current practice in infants with prenatal opioid exposure. We hypothesized that infants treated with M + P would have a shorter length of stay than infants treated with M + C but no difference in the length of opioid treatment.

## METHODS

The Advancing Clinical Trials in Neonatal Opioid Withdrawal (ACT

NOW) Current Experience study is a multicenter observational cross-sectional study of infants with NOWS from 30 hospitals across the United States from July 1, 2016, to June 30, 2017. The ACT NOW Collaborative is a partnership between the Environmental influences on Child Health Outcomes Institutional Development Award States Pediatric Clinical Trials Network and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NRN) and is part of the National Institutes of Health's trans-agency Helping to End Addiction Long-term Initiative. A central Institutional Review Board at the University of Arkansas for Medical Sciences approved the study.

Data were selected for abstraction from medical records by trained research personnel if infants were  $\geq 36$  weeks' gestation and had either NOWS scoring with the Finnegan scoring system or modified Finnegan scoring system within the first 120 hours of life or documented prenatal opioid exposure (maternal history, maternal positive toxicology screen during second or third trimester of pregnancy, and/or infant positive toxicology screen). The Medical Record Abstraction Quality Assurance and Control Framework was used to improve accuracy of data abstraction.<sup>15,16</sup> For this retrospective cohort analysis, we included only infants with both documented NOWS scoring and documented prenatal opioid exposure. Additionally, infants had to have been given morphine as first-line treatment to isolate the effects of phenobarbital versus clonidine as secondary medications in infants with NOWS. All sites dosed morphine every 3 hours, although some sites did have caveats in their morphine-weaning protocols that if the infant was sleeping at the 3-hour mark, the dose could be delayed up to 1 additional hour. The choice of clonidine or phenobarbital was based

on each individual center's usual care and protocol. We chose to include the group of infants treated with morphine only as a reference group.

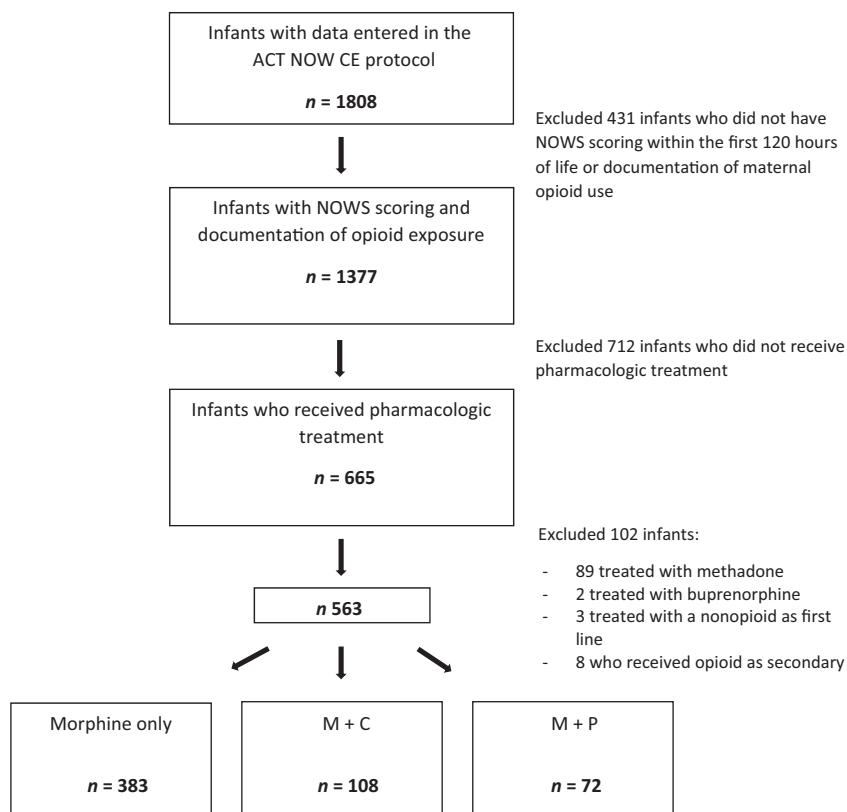
Descriptive statistics were used to characterize and summarize infant and maternal characteristics overall and by infant groups (morphine alone, M + P, and M + C). The mean and SD were reported for continuous variables, and frequencies and percentages were reported for categorical variables. Additionally, the initial descriptive statistics were investigated by using one-way analysis of variance (ANOVA) and  $\chi^2$  test, as appropriate. No adjustments for multiple comparisons were made for the descriptive analysis. Outcomes of interest included length of morphine treatment in days, length of inpatient hospital stay in days, and peak morphine dose in milligrams per kilogram. For each outcome, we compared the group means using one-way ANOVA followed by multivariable linear regression. Covariates with possible impact on each outcome based on previous literature were selected for the multivariable model.<sup>2,17-19</sup> The covariates included were race and ethnicity (defined as non-Hispanic white and other), sex, maternal polysubstance use (defined as mother or infant with a history or positive toxicology screen for substances other than opioids during the second and third trimester, including gabapentin, selective serotonin reuptake inhibitors, and benzodiazepines), maternal opioid (buprenorphine only, methadone only, or other), and hospital NOWS volume (based on number of NOWS cases each site contributed to this study). For our main analysis, we did not include birth weight or gestational age as covariates because all infants in the study were  $\geq 36$  weeks' gestation at birth. We did conduct a sensitivity analysis including birth weight and gestational age as additional confounders. The

results of this model (provided in Supplemental Tables 4 and 5) were unchanged from the results of the main analysis, and therefore birth weight and gestational age were not included to achieve the most parsimonious model. Consistent with the National Institutes of Health initiative to consider sex in data analyses,<sup>20</sup> we examined the potential moderation effect of sex on the relationship between group and each outcome (ie, group-by-sex interaction). Our main analysis used hospital NOWS volume as a fixed effect because there were only a few sites that used both phenobarbital and clonidine, and using a random site effect would place substantial weight on the limited number of observations within those few hospitals, resulting in broad SEs. However, to be sure, we also conducted a subsequent analysis that used a linear mixed model to account for infants nested within site to help determine which observed results from the fixed effects model might be due to unobserved site level differences. To evaluate whether differences in any observed effect would exist across sites, we compared the site with the largest number of M + P observations with the site with the largest number of M + C observations, as well as grouping M + P observations in smaller sites together and comparing them with M + C observations in smaller sites. All outcome variables were tested for normality and departures from normality were minimal. Nonetheless, we conducted sensitivity analyses for all regressions using log-transformed outcomes. The results did not differ from those of the main analysis, so for clarity, the regression results of the nontransformed outcomes are presented.

## RESULTS

Of the 1808 mother-infant dyads in the ACT NOW Current Experience study, 563 infants with documented

prenatal opioid exposure and NOWS scoring received pharmacologic treatment with morphine as first-line therapy and were included in the current study (Fig 1). Of those infants, 180 (32%) also received secondary treatment: 72 (40%) with M + P and 108 (60%) with M + C. No participants received both phenobarbital and clonidine. Only 1 participant received a tertiary medication (methadone) after failure of secondary medication, and this participant was included in the analysis. Four sites used morphine alone or M + P, 7 sites used morphine alone or M + C, 6 sites used all 3 combinations, and 7 sites never used secondary medications, treating infants only with morphine. Sites that only used morphine alone were retained in the analysis to provide greater generalizability and precision of outcome estimates for the group of infants treated with morphine alone. Phenobarbital treatment was continued after discharge in 56 of 72 infants (78%), and 31 of 108 infants (29%) were discharged from the hospital on clonidine,  $P < .0001$ . The time of onset of secondary medication was similar in both groups ( $7 \pm 8.5$  days after morphine start in the phenobarbital group,  $8.5 \pm 7.6$  days after morphine start in the clonidine group,  $P = .072$ ). Thirty-five infants were started on secondary medication on the same day as the primary morphine treatment: 14 in the M + P group (19.4%) and 21 in the M + C group (19.4%). Demographics of each group are shown in Table 1. The average birth weight and gestational age at birth were similar across the groups. Approximately 55% of the infants were male. There was a higher proportion of non-Hispanic white infants in the M + C group compared with the morphine alone group. Infants whose mothers only used methadone as opposed to buprenorphine or other and/or multiple opioids were more likely to



**FIGURE 1**  
Subject flow diagram. CE, Current Experience.

be treated with phenobarbital versus clonidine. Other maternal measures were similar across groups.

As shown in Fig 2, the unadjusted mean length of stay was shorter ( $26.4 \pm 12.4$  days versus  $36.5 \pm 12.6$  days;  $\Delta = -10.04$  days; 95% confidence interval [CI]: 7.08 to 12.99 days;  $P < .0001$ ) and length of morphine treatment shorter ( $20.8 \pm 11.4$  days versus  $28.1 \pm 11.3$  days;  $\Delta = -7.3$  days; 95% CI: 4.51 to 10.07 days;  $P < .0001$ ) for the M + P group compared with the M + C group, but the peak morphine dose was higher in the M + P group compared with the M + C group ( $0.08 \pm 0.05$  mg/kg versus  $0.07 \pm 0.03$  mg/kg;  $\Delta = 0.01$  mg/kg; 95% CI: 0.003 to 0.023 mg/kg;  $P = .01$ ). The length of stay and duration of morphine treatment were longer for infants receiving either secondary medication than for those treated with morphine only ( $P < .0001$ ) (Table 2). After adjusting for race and

ethnicity, sex, maternal polysubstance use, type of maternal opioid,  $>1$  maternal opioid, and hospital volume, length of stay and length of morphine treatment remained shorter in the M + P group compared with the M + C group ( $\Delta_{\text{length of stay}} = -10.26 \pm 1.50$  days; 95% CI  $-13.21$  to  $-7.31$  days;  $\Delta_{\text{morphine treatment}} = -7.51 \pm 1.4$ ; 95% CI  $-10.27$  to  $-4.75$  days;  $P < .0001$  for both), but difference in peak morphine dose was no longer statistically significant at the 0.05 level between the 2 groups. Results from the mixed model using site as a random effect are shown in Table 3. In the mixed model, length of stay remained shorter in the M + P group compared with the M + C group ( $\Delta = -4.07 \pm 1.93$  days; 95% CI:  $-7.86$  to  $-0.27$  days;  $P = .036$ ), but difference in length of morphine treatment and peak morphine dose were no longer significant. Comparison of the site with the largest number of M + P observations and the site with the

largest number of M + C observations were consistent with the results of the main analysis. Directionality of the observed effects among observations in smaller sites were consistent with the main effect, although, because of smaller sample size, statistical significance was not reached. The interaction effects of sex and treatment group were not significant for length of stay or for length of morphine treatment ( $P = .07$  for both). In contrast, for peak morphine dose, the interaction of treatment group and sex was significant ( $P = .01$ ). Further analysis by sex only identified significant differences in peak morphine dose among male infants treated with M + P compared with boys treated with M + C and boys compared with girls treated with M + P. However, no differences between these groups were  $>0.04$  mg/kg and are therefore likely not of clinical significance.

## DISCUSSION

In this large, multicenter, contemporary, observational study, both in unadjusted analyses and after adjusting for relevant covariates, infants with NOWS given M + P had shorter length of hospital stay and shorter length of morphine treatment than infants treated with M + C. When including site as a random effect, difference in length of morphine treatment was no longer significant, suggesting this is not as robust a finding and could be due to site level differences not accounted for in our main model.

Potential benefits of shorter hospitalization include reduced cost and family stress. NICU hospitalizations cost  $\sim$ \$2500 per day, making a 10-day reduction in length of stay financially significant for families and insurance providers. To an extent, our findings support a shorter length of morphine exposure for those treated with phenobarbital, and researchers of

**TABLE 1** Descriptive Summary of Maternal and Infant Characteristics by Group

	All (N = 563)	Morphine Alone (n = 383)	M + P (n = 72)	M + C (n = 108)	P
<b>Infant demographics</b>					
Birth wt, mean (SD), kg	3.0 (0.5)	3.0 (0.5)	3.1 (0.5)	3.1 (0.5)	.190
Gestational age, mean (SD), wk	38.3 (1.4)	38.2 (1.4)	38.6 (1.5)	38.5 (1.3)	.054
Male, n (%)	310 (55.1)	211 (55.1)	43 (59.7)	56 (52.9)	.816
Finnegan score before starting morphine treatment, mean (SD)	10.6 (2.5)	10.7 (2.5)	10.1 (2.5)	10.9 (2.4)	.782
<b>Maternal measures, n (%)</b>					
Non-Hispanic white	389 (69.1)	252 (65.8)	53 (73.6)	84 (77.8)	.040
Buprenorphine only	145 (25.8)	99 (25.9)	13 (18.1)	33 (30.6)	.171
Methadone only	84 (14.9)	52 (13.6)	20 (27.8)	12 (11.1)	.004
>1 opioid	286 (50.8)	199 (52.0)	33 (54.2)	54 (50.0)	.624
Maternal polysubstance use	351 (62.3)	240 (62.7)	52 (72.2)	59 (54.6)	.068
Any breastfeeding	216 (38.4)	156 (40.7)	23 (33.5)	36 (33.3)	.141
<b>Hospital NOWS volume during study period, n (%)</b>					
1 (<30)	54 (9.6)	37 (9.7)	3 (4.2)	14 (13.0)	.214
2 (30–79)	138 (24.5)	100 (26.1)	15 (20.8)	23 (21.3)	—
3 (≥ 80)	371 (66.0)	246 (64.2)	54 (75.0)	71 (65.7)	—

The P values are based on a one-way ANOVA or  $\chi^2$  test comparing across the 3 groups; pairwise comparisons were performed for non-Hispanic white with statistical significance between morphine alone versus M + C ( $P = .02$ ); pairwise comparisons were performed for methadone only with statistical significance between morphine alone versus M + P ( $P = .003$ ) and M + C versus M + P ( $P = .004$ ). —, not applicable.

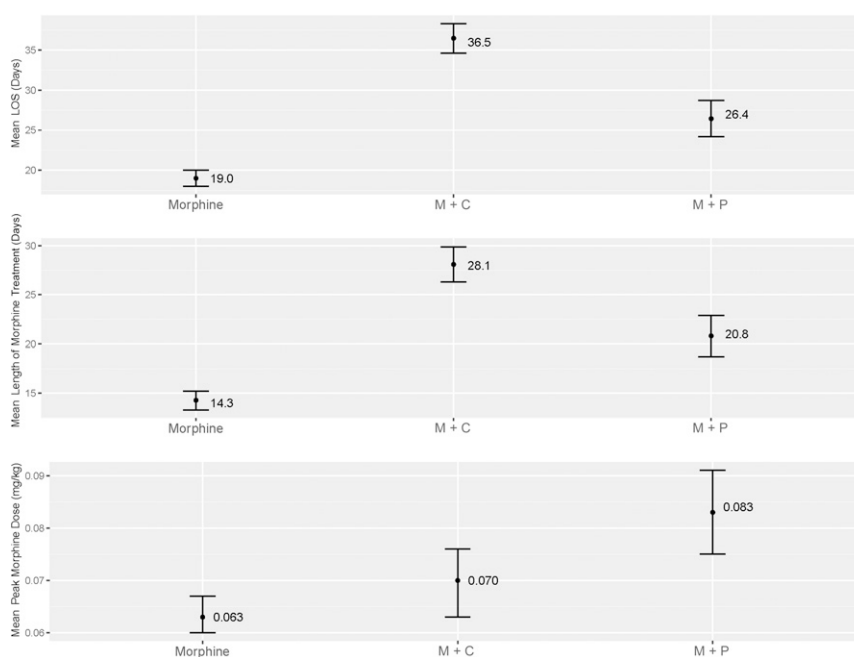
previous studies have demonstrated potential benefits of shorter morphine exposure. Indeed, in vitro studies reveal apoptosis after morphine exposure in human neurons and microglia,<sup>21</sup> animal studies reveal adverse effects of postnatal morphine on neurobehavior,<sup>22</sup> and studies in preterm infants reveal an adverse

association between neonatal morphine exposure and later neurodevelopment.<sup>23</sup>

Yet, more infants in our study cohort were sent home on phenobarbital, likely resulting in a longer total pharmacologic treatment period for NOWS. Although we did not examine postdischarge treatment duration or

neurodevelopment, previous research suggests that most infants are treated with phenobarbital for several months after discharge.<sup>24</sup> Additional or longer exposure to phenobarbital is concerning. Phenobarbital is an inhibitor of the  $\gamma$ -aminobutyric acid type A receptor. Phenobarbital's potent sedative effects decrease some of the neurologic symptoms of NOWS (hyperirritability, sleep disturbances), but phenobarbital does not directly address the pathophysiology of withdrawal.<sup>9</sup> There is concern about side effects of phenobarbital in neonates, particularly oversedation, as well as neuronal apoptosis and long-term neurodevelopmental effects of neonatal phenobarbital treatment seen in both animal<sup>25,26</sup> and human<sup>27</sup> studies. It is unclear to what extent the neurodevelopmental impact seen in previous studies is due to phenobarbital itself versus the large concentration of alcohol in commercially available solutions.

Clonidine has been used in both monotherapy and as adjunctive therapy for NOWS.<sup>28</sup> There has been less concern for clonidine's side effects, although authors of a recent article reported hypotension and rebound hypertension in infants



**FIGURE 2** Comparison of unadjusted group means. Error bars reflect SEs. LOS, length of stay.

**TABLE 2** Results of Multivariable Linear Regression Models

Outcome and Group Comparison	Mean Difference	P	Lower 95% CI	Upper 95% CI
Length of hospital stay				
Morphine versus M + P	-7.22	<.0001	-9.70	-4.75
Morphine versus M + C	-17.48	<.0001	-19.59	-15.38
M + P versus M + C	-10.26	<.0001	-13.21	-7.31
Length of morphine treatment				
Morphine versus M + P	-6.19	<.0001	-8.49	-3.88
Morphine versus M + C	-13.70	<.0001	-15.67	-11.72
M + P versus M + C	-7.51	<.0001	-10.27	-4.75
Peak morphine dose mg/kg				
Morphine versus M + P	-0.017	<.0001	-0.026	-0.008
Morphine versus M + C	-0.008	.037	-0.015	-0.0005
M + P versus M + C	0.010	.072	-0.0008	0.019

Morphine; M + P; M + C; covariates included race and ethnicity, infant sex, maternal polysubstance use; type of maternal opioid, >1 opioid, and hospital volume.

treated with clonidine for NOWS.<sup>13</sup> Clonidine as a secondary therapy to morphine has been shown to reduce the duration of opioid therapy compared with placebo<sup>29</sup> in a randomized controlled trial, with no increase in adverse outcomes (hypotension, rebound hypertension, bradycardia, or desaturations). There has also been interest in clonidine as monotherapy versus morphine, with researchers in 1 small study<sup>30</sup> showing decreased length of treatment in the clonidine group. The clonidine group also had improved neurobehavior using the NICU Network Neurobehavioral Scale at 40 to 44 weeks postmenstrual age, although Bayley Scales of Infant Development at 1 year of age did not differ between groups. We found that, overall, infants treated with M + C had a lower peak morphine dose than those treated with M + P in unadjusted analysis, but this may

have been due to confounding, and the result did not meet statistical significance after adjustment.

Our results align with the 2013 Surran et al<sup>12</sup> and 2020 Brusseau et al<sup>13</sup> randomized controlled trials of phenobarbital versus clonidine as secondary treatments for NOWS. Although these studies were small (Surran, 68 infants total and Brusseau, 25 infants total) and differed in design (Surran randomly assigned infants to M + P or M + C when initially starting treatment, Brusseau randomly assigned infants to phenobarbital or clonidine after failure of morphine), our study suggests that their results do generalize to a larger and broader population of infants and that using phenobarbital as a secondary medication, although usually continued after discharge, does allow for shorter length of stay. Our results

contrast with the 2017 study by Devlin et al<sup>14</sup> in which phenobarbital and clonidine were retrospectively compared as adjuvant treatments but with variable dosing intervals of morphine. In their study, they found that infants treated with morphine every 3 hours plus clonidine had shorter length of treatment and hospital stay than infants treated with morphine every 4 hours plus phenobarbital, with all medications weaned off before hospital discharge. It is unclear whether the shorter morphine dosing interval or their practice of weaning off all medications before discharge contributed to their findings, and this raises the question of whether the larger proportion of infants discharged from the hospital on phenobarbital in our study was the primary driver for shorter hospital stay. This underscores the need for a study of secondary NOWS

**TABLE 3** Results of Multivariable Linear Mixed Regression Models

Outcome Group Comparison	Mean Difference	P	Lower 95% CI	Upper 95% CI
Length of hospital stay				
Morphine versus M + P	-13.15	<.0001	-16.18	-10.11
Morphine versus M + C	-17.22	<.0001	-19.71	-14.73
M + P versus M + C	-4.07	.036	-7.86	-0.27
Length of morphine treatment				
Morphine versus M + P	-11.75	<.0001	-14.54	-8.96
Morphine versus M + C	-13.47	<.0001	-15.77	-11.16
M + P versus M + C	-1.71	.337	-5.22	1.79
Peak morphine dose, mg/kg				
Morphine versus M + P	-0.022	<.0001	-0.032	-0.011
Morphine versus M + C	-0.015	.0006	-0.024	-0.0007
M + P versus M + C	0.007	.324	-0.007	0.020

Morphine; M + P; M + C; covariates included race and ethnicity, infant sex, maternal polysubstance use; type of maternal opioid, and >1 opioid.

treatments that includes data collection after discharge as well as long-term follow-up.

The strengths of our study include a large multicenter cohort of infants with standardized collection of observational data. The limitations of our study include the issues inherent in medical record review and retrospective multicenter studies, including the lack of standardized treatment and care protocols among sites and the lack of randomization. We are also limited by the fact that only a few centers routinely used M + C or M + P, which increases the chance that a nonidentified confounder could have influenced our findings. We did not have information on social barriers to discharge affecting length of stay, potential medication side effects, and postdischarge outcomes (including medication discontinuation, readmissions, and neurodevelopment). It is also possible we were unable to account for practice differences between centers in our models, or that larger centers may have contributed more strongly to the overall effect.

## CONCLUSIONS

In this study, infants treated with M + P had substantially shorter length of hospital stay and, potentially, fewer days of morphine treatment. However, the benefits of phenobarbital over clonidine as a secondary medication to morphine must be weighed against the possible long-term adverse neurodevelopmental effects of phenobarbital continuation after discharge. Further research should focus on the development of optimal nonpharmacologic care and pharmacologic treatment regimens that reduce length of hospital stay, length of morphine treatment, and peak morphine dosing while protecting long-term neurodevelopmental outcomes.

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#### ABBREVIATIONS

ACT NOW: Advancing Clinical Trials in Neonatal Opioid Withdrawal  
ANOVA: analysis of variance  
CI: confidence interval  
M + C: morphine plus clonidine  
M + P: morphine plus phenobarbital  
NOWS: neonatal opioid withdrawal syndrome  
NRN: Neonatal Research Network

The data set supporting the conclusions of this article is available by request to the corresponding author through a data use agreement and will be uploaded into a publicly available repository within 6 months of publication.

Drs Merhar, Das, Devlin, Higgins, Lester, Poindexter, Simon, P. Smith, and Young made substantial contributions to the conception and design of the study and drafting of the manuscript; Drs Fuller, Sanchez, and Whalen contributed to the design of the data collection forms and data acquisition; Dr Ounpraseuth and Ms Thombre conducted statistical analysis, provided interpretation of the data, substantially contributed to the methods and results sections of the manuscript, and created graphics; Drs Berkeley, Crowley, Czysnski, Kiefer, Newman, and M. Smith helped with acquisition of data, and provided input on data interpretation; and all authors reviewed the manuscript for important intellectual content and have approved the final version for publication. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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