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ORIGINAL ARTICLE

Efficacy of clonidine versus phenobarbital in reducing neonatal morphine sulfate therapy days for neonatal abstinence syndrome. A prospective randomized clinical trial

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OBJECTIVE: To compare the efficacy of clonidine versus phenobarbital in reducing morphine sulfate treatment days for neonatal abstinence syndrome (NAS).

STUDY DESIGN: Prospective, non-blinded, block randomized trial at a single level III NICU (Neonatal Intensive Care Unit). Eligible infants were treated with a combination of medications as per protocol. Primary outcome was treatment days with morphine sulfate. Secondary outcomes were the mean total morphine sulfate dose, outpatient phenobarbital days, adverse events and treatment failures.

RESULTS: A total of 82 infants were eligible, of which 68 were randomized with 34 infants in each study group. Adjusting for covariates phenobarbital as compared with clonidine had shorter morphine sulfate treatment days (-4.6, 95% confidence interval (CI): -0.3, -8.9; $P=0.037$) with no difference in average morphine sulfate total dose (1.1 mg kg^{-1}, 95% CI: -0.1, 2.4; $P=0.069$). Post-discharge phenobarbital was continued for an average of 3.8 months (range 1 to 8 months). No other significant differences were noted.

CONCLUSION: Phenobarbital as adjunct had clinically nonsignificant shorter inpatient but significant overall longer therapy time as compared with clonidine.

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INTRODUCTION

Neonatal abstinence syndrome (NAS) is likely to occur in 55 to 94% of neonates exposed to intrauterine opioids.[1,2] NAS results in neurological symptoms, as well as enteric, sympathetic and parasympathetic dysregulation.[3] There has been a significant increase nationwide in infants treated for NAS with associated increase in health-care costs.[4] Multiple and variable drug exposures can lead to NAS,[5–9] and treatment frequently requires inpatient pharmacotherapy with opioids and adjunctive medications. Recent studies suggest that combination therapies to treat NAS are superior to opioid replacement alone.[10,11] This may in part be due to variability in the severity of NAS either because of the genetic predisposition[12] or because of increasing polydrug use in the mothers.[13] Phenobarbital may reduce withdrawal symptom severity, length of hospitalization and hospital costs.[10,14,15] However, there are concerns about the long-term outcomes from prolonged phenobarbital exposure on the developing neonatal brain. Animal models suggest inhibited neurogenesis and survival,[16] whereas human studies have shown neurodevelopmental and behavioral compromises.[17] Clonidine, a centrally acting alpha$_2$-adrenergic receptor agonist, by reducing the sympathetic outflow directly influences NAS symptoms and has been shown to be a safe, effective adjunct while reducing length of treatment.[11,18–21] However, currently no comparative studies are available for phenobarbital and clonidine when used as an adjunct to neonatal morphine sulfate for treatment of NAS. The current trial was therefore set up to compare the efficacy of clonidine versus phenobarbital as an adjunct medication to neonatal morphine sulfate for infants with NAS.

METHODS

This was a prospective, non-blinded, single site and randomized clinical trial for infants undergoing moderate to severe NAS. The purpose of the study was to compare the efficacy of clonidine (NMS/C) versus phenobarbital (NMS/P) in reducing morphine sulfate (NMS) treatment days for infants with NAS. The primary null hypothesis was that there would be no difference in treatment approaches. Our alternative hypothesis was that NMS/C would be more efficacious by an average of 5 days in comparison to the NMS/P.

Inclusion/exclusion criteria

Any infant with a suspected or confirmed maternal history of opioid or illicit drug use during the pregnancy was screened for eligibility and a comprehensive urine toxicology sample was sent from the first void. Eligible infants were $\leqslant$15 days old, with prenatal opioid exposure, moderate to severe NAS defined as two consecutive Modified Finnegan Scores (MFS) $\geqslant$8, and medically stable. Modified Finnegan Scoring is one of the validated tools used routinely for assessing withdrawal severity.[3] Infants with a gestational age (GA) of $<$35 weeks, intrauterine growth retardation (birth weight $<$5th percentile for GA), congenital anomalies, known exposure to benzodiazepines *in utero* and medically unstable were excluded.

The study was conducted at Baystate Children's Hospital, Davis Neonatal Intensive Care Unit (NICU), a level III, regional perinatal referral center, for

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Western Massachusetts, from June 2010 to June 2012. Institutional Review Board approval for the study and written informed parental or legal guardians' consent were obtained prior to enrollment. All at-risk infants were initially cared for in the newborn nursery as per the normal newborn nursery protocols. Additional care for these at-risk infants included monitoring for NAS using MFS every 3 to 4 h, in the newborn nursery. Our hospital has been using this scoring system for over a decade and the nursing staff are routinely validated on their scoring skills. However, realizing that this was a non-blinded study and scorer variability could be a potential confounding bias, the study-related nurses were re-validated prior to clinical trial commencement. MFS for all enrolled infants were electronically documented by trained nursing staff every 3 h; this guided initiation, dose adjustments and weaning of the study medications.

If infants met the enrollment criteria, parents were approached for consent. Once enrolled in the study, infants were transferred to the NICU where the infants were re-scored for confirmation and determination of the initial medication doses. The standard protocol used in the NICU utilized the MFS to guide escalation and de-escalation of morphine sulfate (Table 1). The morphine sulfate solution concentration was 0.4 mg ml^{-1}, a standard formulation used in the NICU. The clonidine suspension used was 10 mcg ml^{-1} and phenobarbital suspension was 4 mg ml^{-1}. The doses for both the adjunct medications were based on the MFS as well as previously published studies.[11] If after initiation of clonidine, bradycardia and/or hypotension was noted, the dose was decreased to the next lower dose until the vital signs stabilized. Infants were maintained on original pharmacotherapy dosage for 48 h following initiation to bring the withdrawal symptoms under control, that is, all scores in the preceding 24-h period were <8. Each infant then had the morphine sulfate dose reduced once in 24 h by 10% of absolute dose if the MFS remained <8 and was discontinued at 0.12 mg kg^{-1} per day, as was the pre-trial standard practice in the NICU. If an infant developed recurrence of symptoms with two consecutive NAS scores >8 over a 24-h period following the wean, then the dose was held at the current level. However, if two consecutive scores were significantly higher (>10) then the morphine sulfate dose was increased to the last effective dose. Infants were continued on clonidine at the last effective dose until the morphine sulfate was successfully weaned for 24 h, then it was weaned by 50% in a two-step reduction every 24 h until being discontinued (Table 2). The stepwise wean of clonidine dose was performed to prevent the occurrence of rebound hypertension and sympathetic overactivity. After clonidine was discontinued, the infants were monitored for 36 to 48 h off all medications prior to being discharged home. Phenobarbital was not weaned during the hospital stay and infants were discharged home to be weaned by the primary pediatric provider in the outpatient setting as per the standard practice in the NICU. Infant care in the NICU followed standard care protocols, which included but was not limited to continuous heart rate and respiratory rate monitoring. Additionally, the clonidine group had blood pressure (BP) measured every 6 h for first 48 h, followed by every 12 h until they weaned from morphine sulfate. Once off the morphine sulfate, BP was monitored every 6 h during the clonidine weaning to ensure stable BP. As blood pressure variations have not been reported with phenobarbital use within therapeutic range, and were not done routinely in our standard pre-trial protocol, this group did not have their BP monitored unless clinically indicated.

Study outcomes and adverse events

The primary endpoint of the study was the time taken to wean the infants off morphine sulfate in the two groups. Although time taken for full completion of neonatal abstinence therapy would have been ideal, we chose the time taken to wean off morphine sulfate as the primary outcome measure, as infants were discharged home on phenobarbital, whereas infants stayed additional inpatient days to wean off clonidine. Thus, time-to-wean off of morphine sulfate was considered a more appropriate measure of efficacy comparison. Secondary outcomes included total dose of morphine sulfate required, total phenobarbital treatment days, total number of treatment failures, any adverse events, mortality in the hospital and re-admission in 1 week post discharge. Adverse events were predefined measures for each group. For phenobarbital sedation, seizures, any cardiovascular arrhythmia and bradycardia (sustained heart rate <80 beats min^{-1}) were monitored. For the clonidine group in addition to above, any evidence of hypotension (mean BP <2 SD. for GA) and hypertension (mean BP >2 SD for GA) was also recorded.

Baystate Health Institutional Review Board provided study oversight. Additionally, the study methods required data analysis mid-way during the study to assess for any unintended adverse events.

Randomization and blinding

Infants were randomly assigned by the statistical team to one of the two combination groups: morphine sulfate and clonidine (NMS/C) versus morphine sulfate and phenobarbital (NMS/P). The clinical research team was blinded to randomization. Assignment was under equal allocation according to a computer-generated randomization procedure in blocks of 4 and 6. To ensure balance on important patient characteristics, randomization was stratified on maternal drug history (single drug use versus polydrug use); this did not include alcohol or smoking. The randomization list was generated by the Epidemiology and Biostatistics Research Core located within the Institution.

Different dosing intervals and additional clinical monitoring of the infants in the clonidine group prevented us from conducting a blinded study. However, clinicians involved in the study followed a strict protocol for treatment and weaning procedures. Further, the PI remained blinded to treatment assignment in providing clinical oversight, and the interim statistical analysis was conducted in a blinded manner.

Statistical analysis

Univariable comparisons of continuous data across study groups were reported as medians and range and compared using Wilcoxon rank-sum test. Categorical data were compared using Fisher's exact test. Multivariable analyses were conducted using a generalized linear model to account for skewness in the distribution of treatment days.[22] Multivariable models included polydrug status, GA, gender, MFS, baseline treatment dose, maternal age, and 5-minute Apgar score. We note that two infants (one in each study group) were missing Apgar scores at baseline. Imputed values for the missing scores were derived from a linear regression model including group assignment, polydrug status, GA, gender, MFS, baseline treatment dose, and maternal age. Analyses were conducted in Stata (version 12.1, StataCorp, College Station, TX). All analyses were intent-to-treat.

Sample-size estimation. Sample size was estimated using the PASS program (version 2008, J Hintze, Kaysville, UT, USA). Calculations used estimates of variability from historical clinic data. A 5-day difference in NMS duration was considered clinically meaningful. A fixed sample size of

Table 1. Dosing protocol for the two study groups

Finnegan score	*NMS-C treatment group*[a]	*NMS-P treatment group*
8–10	Morphine sulfate 0.32 mg kg^{-1} per day divided q3h PLUS clonidine 6 mcg kg^{-1} per day divided q6h	Morphine sulfate 0.32 mg kg^{-1} per day divided q3h PLUS phenobarbital 6 mg kg^{-1} per day divided q8h
11–13	Morphine sulfate 0.48 mg kg^{-1} per day divided q3h PLUS clonidine 8 mcg kg^{-1} per day divided q6h	Morphine sulfate 0.48 mg kg^{-1} per day divided q3h PLUS phenobarbital 8 mg kg^{-1} per day divided q8h
14–16	Morphine sulfate 0.64 mg kg^{-1} per day divided q3h PLUS clonidine 10 mcg kg^{-1} per day divided q6h	Morphine sulfate 0.64 mg kg^{-1} per day divided q3h PLUS phenobarbital 10 mg kg^{-1} per day divided q8h
$\geqslant$17	Morphine sulfate 0.8 mg kg^{-1} per day[b] divided q3h PLUS clonidine 12 mcg kg^{-1} per day divided q6h	Morphine sulfate 0.8 mg kg^{-1} per day[b] divided q3h PLUS phenobarbital 12 mg kg^{-1} per day divided q8h

[a]Clonidine escalation may be limited by hypotension or bradycardia.
[b]If requirement of morphine sulfate >0.8 mg kg^{-1} per day, increase dose in increments of 0.16 mg kg^{-1} per day until Finnegan score is <8.

Table 2. Weaning protocol for clonidine

Starting clonidine daily dose	*First clonidine weaning dose*	*Second clonidine weaning dose*	*Third weaning step*
6 mcg kg^{-1} per day	3 mcg kg^{-1} per day × 24 h	1.5 mcg kg^{-1} per dose × 24 h	Discontinue clonidine
8 mcg kg^{-1} per day	4 mcg kg^{-1} per day × 24 h	2 mcg kg^{-1} per day × 24 h	Discontinue clonidine
10 mcg kg^{-1} per day	5 mcg kg^{-1} per day × 24 h	2.5 mcg kg^{-1} per day × 24 h	Discontinue clonidine
12 mcg kg^{-1} per day	6 mcg kg^{-1} per day × 24 h	3 mcg kg^{-1} per day × 24 h	Discontinue clonidine

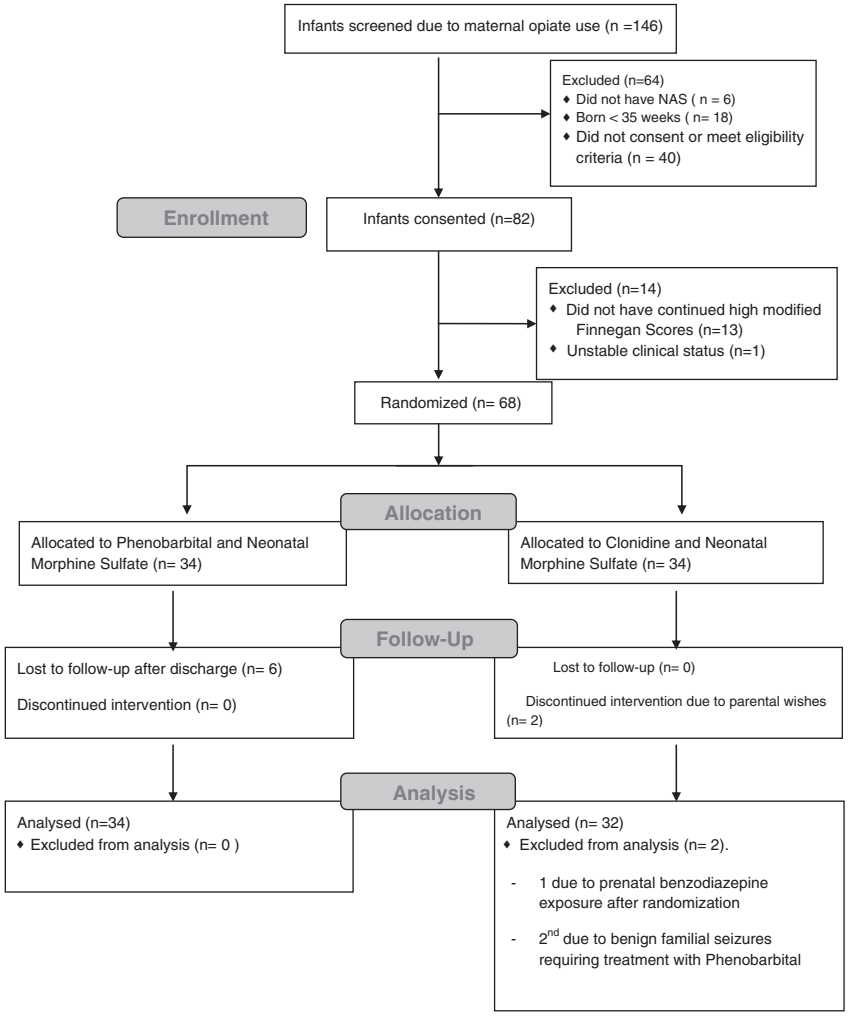

Figure 1. Screening, randomization and rate of treatment completion, according to the study group.

55 patients per study group was determined to provide 87% power to detect a 5-day difference in the mean treatment time between study groups, assuming a standard deviation of about 8.5 days for a two-sided comparison of the group means at a critical level of 5%. The above estimates were computed anticipating one interim look when at least 50% of patients had been enrolled.

Early termination. We evaluated whether to terminate the study for the lack of efficacy at the interim analysis following team review. Interim analysis indicated a difference in the mean treatment time of 5.4 days (±8.5 days). Contrary to our expectation, however, the difference favored NMS/P. Further, using the approach described by Proschan *et al.*,[23] we computed conditional power for two scenarios: (1) under the originally hypothesized assumptions of group difference and variability and, (2) under the results observed at the interim analysis. For each scenario, conditional power favoring the NMS/C group was <1%. Given our initial clinical expectation and the very low conditional power for our hypothesis,[24] we terminated for the lack of efficacy at the interim analysis.

RESULTS

During the study period, 146 mothers were identified with a documented history of recreational drug use, excluding alcohol and smoking; of these, 6 did not experience NAS, 18 delivered at <35 w GA and 40 were in the group of not-meeting-eligibility. They were either transferred from another hospital already receiving treatment or refused consent and were excluded. Parents/guardians of 82 infants consented to the study, of which 68 were randomized, with 34 infants randomized to each study arm (Figure 1). Two infants in the NMS/C group were withdrawn from the study: one had benzodiazepine exposure *in utero* identified subsequent to enrollment; the second had a seizure while in the study, requiring phenobarbital treatment. The seizure was diagnosed as benign familial seizure unrelated to NAS.

Mothers in our cohort were older, multigravid females with a high number of polydrug use and were either in rehabilitation

Table 3. Baseline characteristics of study groups

Characteristic	*Phenobarbital* (n = *34*)		*Clonidine* (n = *32*)		P-*value*
	Mean	*(s.d.)*	*Mean*	*(s.d.)*	
Gestational age (weeks)	38.6	(1.7)	39.2	(1.4)	0.11
Birth weight (g)	3075.0	(476.0)	3,217.8	(488.0)	0.23
Head circumference (cm)	33.5	(1.8)	33.8	(1.8)	0.58
Apgar at 5 min	8.8	(0.4	8.7	(0.6)	0.38
Maternal age	28.1	(4.6)	28.2	(4.8)	0.91
Gravida	3.4	(2.5)	3.6	(2.2)	0.76
Age at diagnosis (months)	2.3	(1.6)	1.8	(0.9)	0.17
Modified Finnegan score	11.9	(2.1)	13.4	(3.2)	0.03
	Median	*(Min, max)*	*Median*	*(min, max)*	
Methadone dose[a]	110.0	(5, 243)	112.5	(75, 188)	0.51
Buprenorphine dose[b]	8.0	(2, 24)	8.0	(2, 20)	0.42
Oxycodone dose[c]	27.5	(10, 40)	90	(40, 125)	0.03
	%	*(n)*	*%*	*(n)*	
Male gender	52.9	(18)	46.9	(15)	0.81
Breast milk	26.5	(9)	25.0	(8)	>0.99
Formula	94.1	(32)	96.9	(31)	>0.99
Alcohol use	2.9	(1)	3.1	(1)	>0.99
Smoker	55.9	(19)	56.3	(18)	>0.99
Vaginal delivery	67.6	(23)	75.0	(24)	0.59
Methadone use	47.1	(16)	31.3	(10)	0.22
Buprenorphine use	32.4	(11)	53.1	(17)	0.14
Oxycodone use	23.5	(8)	25.0	(8)	>0.99
Polydrug use	41.2	(14)	40.6	(13)	>0.99

[a]Phenobarbital: $n = 16$; Clonidine: $n = 10$.
[b]Phenobarbital: $n = 11$; Clonidine: $n = 14$.
[c]Phenobarbital: $n = 6$; Clonidine: $n = 3$.

secondary to or were abusing oxycodone at the time of delivery. There were no significant differences in baseline characteristics except for a trend towards higher NAS scores (*P*-value = 0.08) and a higher maternal oxycodone dose (*P*-value = 0.03) in the NMS/C group (Table 3).

Primary outcome

Univariable and multivariable results for primary outcome are shown in Table 4. In the unadjusted analysis, NMS/C had higher mean treatment days than NMS/P (unadjusted 7.1 days, 95% confidence interval (CI): 2.7, 11.4; $P = 0.001$). Multivariable analyses using general linear model regression adjusted for polydrug status, GA, gender, MFS, baseline treatment dose, maternal age and 5-min Apgar score. Results showed an adjusted mean difference in the study groups of 4.6 days, (95% CI: 0.3, 8.9; $P = 0.03$), favoring the NMS/P group. The NMS/P group thus had fewer morphine sulfate treatment days when compared with NMS/C.

Secondary outcomes

The average total dose of neonatal morphine sulfate between the two groups was similar (1.1 mg kg^{-1}, 95% CI: −0.1, 2.4; $P = 0.069$). For infants in the phenobarbital group, post-discharge follow-up was available for 28 infants. Post-discharge phenobarbital was continued for an average of 3.8 months (range 1 to 8 months).

Two NMS/C infants failed NMS-weaning attempts. These infants were switched to phenobarbital for the remainder of the therapy. No failures occurred in NMS/P. The difference in failed attempts was not statistically significant ($P = 0.23$).

In the phenobarbital group, three infants (8.8%) manifested over sedation signs (poor feeds and mild respiratory depression). This prompted serum phenobarbital measurements that were noted to be supratherapeutic (>40 mg dl^{-1}) and required dosage adjustment. The difference was not statistically significant ($P = 0.23$).

There were no arrhythmias or abnormal BPs observed (hypo- or hypertension) in the clonidine group.

For both the groups, there was no inpatient mortality and none of these infants were re-admitted to the hospital within 1 week post discharge.

DISCUSSION

This is the first large randomized trial comparing the efficacy of clonidine and phenobarbital as an adjunct to primary opioid therapy for NAS. We found that for both the study groups, the length of treatment days with morphine sulfate was shortened significantly as compared with the pre-trial of average 25 days. We presume that simply having a protocol in place alone may account for the difference.[14] This may make a case for having standardized unit protocols to more effectively treat NAS and remove variability in individual practices.

Our study notes that, although phenobarbital as an adjunct shortened the length of inpatient treatment days with morphine sulfate as compared with clonidine by a clinically nonsignificant number, the overall length of NAS treatment was shorter with clonidine as no outpatient therapy was required once the infant was discharged home. Infants discharged home on phenobarbital continued on it for up to as long as 8 months. This is comparable to the previously published data by other authors who have noted prolonged outpatient therapy with phenobarbital.[10] Such extended treatment increases the concerns about the potential adverse effects phenobarbital may have on the developing neonatal brain as well as the added complexity of

Table 4. Univariable and multivariable regression estimates of outcomes

Outcome	*Univariable* (n = *66*)		*Multivariable* (n = *64*)	
	Estimate (95% CI)	P-*value*	*Estimate (95% CI)*	P-*value*
Average NMS treatment days				
Phenobarbital	12.4 (10.1, 14.7)		13.6 (11.0, 16.1)	
Clonidine	19.5 (15.7, 23.2)		18.2 (14.9, 21.5)	
Difference	7.1 (2.7, 11.4)	0.001	4.6 (0.3, 8.9)	0.037
Total NMS treatment dose (mg kg^{-1})				
Phenobarbital	3.8 (2.9, 4.7)		4.6 (3.8, 5.4)	
Clonidine	6.7 (5.1, 8.3)		5.7 (4.7, 6.8)	
Difference	2.9 (1.1, 4.7)	0.002	1.1 (−0.1, 2.4)	0.069

Abbreviation: CI, confidence interval.

continued therapy in the home environment with multiple follow-ups with the primary care providers to monitor and adjust the medication dosage for months.

Over the last few decades, the face of addiction has changed dramatically with a whole host of new psychoactive agents in addition to opioids being available with potential for abuse. Prescription drug abuse is on the rise, not only because of the increased focus on pain management but also because of the ease of getting these medications off the street.[13] This brings with it concerns about poor perinatal and long-term neurodevelopmental outcomes for the exposed infants. Moreover, a significant increase in the number of infants admitted to the hospital for treatment of NAS and related health-care costs has been noted.[4]

Even though there are concerns with opioid use for treatment of NAS,[25] the recommendations of the American Academy of Pediatrics note that opioids are the main stay for use as first-line agents for management of NAS due to their ability to control withdrawal symptoms.[14] However, because of the significant variability in the severity of NAS due to the multiple classes and the higher-than-recommended dosing of maternal medications,[12,14] as seen in our maternal cohort, other medications are being evaluated as adjuncts to opioids for more efficient therapy. Of these, clonidine and phenobarbital are the two commonly used adjunct medications. Phenobarbital, which acts as a sedative because of its actions at gamma-aminobutyric acid receptors in the central nervous system, is one such adjunct and is preferred for the treatment of NAS resulting from benzodiazepine or benzodiazepine/opioid dependence.[26] Coyle *et al.*[10,27] demonstrated that phenobarbital with tincture of opium versus tincture of opium alone reduced hospitalization duration and cost, as well as neurobehavioral scores. However, the most notable concern is the impact of prolonged phenobarbital use on the developing neonatal brain,[28–32] which may have long-term cognitive[31] and psychiatric[32] consequences. Although this has not been specifically shown for the subset of infants undergoing NAS therapy, the assumption may be made that brain maturation pathways are similar as for healthy term newborns. Additionally, concerns remain about oversedation secondary to ethanol-containing preparations,[33] its limited effect on GI symptoms and seizure occurrence.

Clonidine, a centrally acting alpha$_2$-adrenergic agonist, activates inhibitory neurons leading to a reduction in sympathetic outflow, thereby helping control NAS. Agthe *et al.*[11] found that clonidine decreases NAS duration compared with placebo and is safe with relatively rare adverse events. Most common adverse effects secondary to clonidine use are sedation, hypotension and bradycardia. Abrupt discontinuation of clonidine may produce manifestations of sympathetic overactivity including increases in blood pressure and heart rate, tremors, agitation and diaphoresis.[34] These adverse reactions can be prevented by tapering the dose downward at discontinuation of therapy. Prolonged outpatient therapy after the discontinuation of opioid treatment is not necessary. Clonidine therapy is not the treatment of choice in cases of maternal dependence on benzodiazepines, sedative–hypnotics or combined benzodiazepine/opioid or hypnotic/opioids, in which phenobarbital maybe more effective and the preferred treatment of choice. Absent contraindications, clonidine's advantages include excellent bioavailability and ethanol-free suspension, [34,35] and it should be considered as an alternative to phenobarbital while considering combination therapies.

Certainly, earlier discharge may have a larger impact on total health-care costs as compared with continued outpatient pharmacotherapy. However, as with any medication used in infants, we must be ever sensitive to the effect an intervention may have during critical periods of brain development. Saving costs at the expense of causing potential harm needs to be avoided. With the robust emerging evidence establishing the negative consequences of medications as phenobarbital on developing brain growth, clinicians have to be cautious while balancing use of such medications with the costs. Although this was not within the purview of our study, when calculating the cost analyses one needs to balance the cost of additional inpatient days with the cost of months of outpatient therapy, follow-up visits and the costs for managing the potential neurocognitive and behavioral disorders that may arise from exposure to phenobarbital.

Additionally, in our study groups there was no difference in the total NMS dose required, suggesting that both the drugs were equally efficacious in controlling NAS symptoms. We also confirmed the findings of the previous studies that used judiciously per standard protocol guidelines clonidine is a safe medication for treating infants experiencing NAS. We did not find any adverse effects with clonidine. There were two treatment failures in this group, requiring transitioning to phenobarbital but this was not a significant difference. It does re-enforce the idea of having standardized protocols for treatment of NAS, clearly defining and personalizing the treatment options for each individual infant. Our unit after the study completion developed a new set of clinical care guidelines with this idea in mind (Supplementary Appendix 1). In the phenobarbital group, over sedation was noted in three infants with supratherapeutic serum levels, requiring downward titration of the dose but this was not statistically significant. However, we would like to recommend that if phenobarbital is used the levels should be monitored to keep them within the therapeutic range.

One of the major limitations to our study was the inability to blind the two groups for the study medications. Different dosing units (μg versus mg), intervals and additional clinical monitoring of the infants in the clonidine group prevented us from

conducting a blinded study. However, with scorer validation, consistent nursing care, weaning decisions made by the medical teams taking care of the infants and strict adherence to the study protocol, we tried to minimize any biases that may have arisen.

In conclusion, our study provides further support to the use of clonidine as an alternative to phenobarbital as an adjunct to primary opioid for treatment of NAS, as it has borne out as both safe and effective within the scope of this study. It provides the advantage of rapid weaning of opioid preparations while also allowing the infant to fully complete treatment prior to discharge.

Further studies regarding the long-term effects of NAS treatment with clonidine are needed in order to adequately compare neurocognitive and behavioral outcomes in children as they grow and develop.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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