JAMA Pediatrics | Original Investigation

Efficacy of a Vibrating Crib Mattress to Reduce Pharmacologic Treatment in Opioid-Exposed Newborns
A Randomized Clinical Trial

Elisabeth Bloch-Salisbury, PhD; James D. Wilson, PhD; Nicolas Rodriguez, BS; Tory Bruch, MPH; Lauren McKenna, BS; Matthew Derbin, MPH; Barbara Glidden, BS; Didem Ayturk, MS; Sanjay Aurora, MD; Toby Yanowitz, MD; Bruce Barton, PhD; Mark Vining, MD; Sue R. Beers, PhD; Debra L. Bogen, MD

IMPORTANCE Pharmacologic agents are often used to treat newborns with prenatal opioid exposure (POE) despite known adverse effects on neurodevelopment. Alternative nonpharmacological interventions are needed.

OBJECTIVE To examine efficacy of a vibrating crib mattress for treating newborns with POE.

DESIGN, SETTING, AND PARTICIPANTS In this dual-site randomized clinical trial, 208 term newborns with POE, enrolled from March 9, 2017, to March 10, 2020, were studied at their bedside throughout hospitalization.

INTERVENTIONS Half the cohort received treatment as usual (TAU) and half received standard care plus low-level stochastic (random) vibrotactile stimulation (SVS) using a uniquely constructed crib mattress with a 3-hour on-off cycle. Study initiated in the newborn unit where newborns were randomized to TAU or SVS within 48 hours of birth. All infants whose symptoms met clinical criteria for pharmacologic treatment received morphine in the neonatal intensive care unit per standard care.

MAIN OUTCOMES AND MEASURES The a priori primary outcomes analyzed were pharmacotherapy (administration of morphine treatment [AMT], first-line medication at both study sites [number of infants treated], and cumulative morphine dose) and hospital length of stay. Intention-to-treat analysis was conducted.

RESULTS Analyses were performed on 181 newborns who completed hospitalization at the study sites (mean [SD] gestational age, 39.0 [1.2] weeks; mean [SD] birth weight, 3076 (489) g; 100 [55.2%] were female). Of the 181 analyzed infants, 121 (66.9%) were discharged without medication and 60 (33.1%) were transferred to the NICU for morphine treatment (31 [51.7%] TAU and 29 [48.3%] SVS). Treatment rate was not significantly different in the 2 groups: 35.6% (31 of 87 infants who received TAU) and 30.9% (29 of 94 infants who received SVS) (P = .60). Adjusting for site, sex, birth weight, opioid exposure, and feed type, infant duration on the vibrating mattress in the newborn unit was associated with reduction in AMT (adjusted odds ratio, 0.88 hours per day; 95% CI, 0.81-0.93 hours per day). This translated to a 50% relative reduction in AMT for infants who received SVS on average 6 hours per day. Among 32 infants transferred to the neonatal intensive care unit for morphine treatment who completed treatment within 3 weeks, those assigned to SVS finished treatment nearly twice as fast (hazard ratio, 1.96; 95% CI, 1.01-3.81), resulting in 3.18 fewer treatment days (95% CI, −0.47 to −0.04 days) and receiving a mean 1.76 mg/kg less morphine (95% CI, −3.02 to −0.50 mg/kg) than the TAU cohort. No effects of condition were observed among infants treated for more than 3 weeks (n = 28).

CONCLUSIONS AND RELEVANCE The findings of this clinical trial suggest that SVS may serve as a complementary nonpharmacologic intervention for newborns with POE. Reducing pharmacotherapy with SVS has implications for reduced hospitalization stays and costs, and possibly improved infant outcomes given the known adverse effects of morphine on neurodevelopment.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02801331

JAMA Pediatr. doi:10.1001/jamapediatrics.2023.1077
Published online May 15, 2023.

Supplemental content

Author Affiliations: Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (Bloch-Salisbury, Wilson, Beers); Department of Pediatrics, University of Massachusetts Chan School of Medicine, Worcester (Bloch-Salisbury, Rodriguez, McKenna, Derbin, Glidden, Aurora, Vining); Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (Bruch, Yanowitz, Bogen); Department of Quantitative and Health Sciences, University of Massachusetts Chan School of Medicine, Worcester (Ayturk, Barton)
.

Corresponding Author: Elisabeth Bloch-Salisbury, PhD, Department of Psychiatry, University of Pittsburgh School of Medicine, 3501 Forbes Ave, Pittsburgh, PA 15213 (salisburye2@upmc.edu).

Newborns with prenatal opioid exposure (POE) present with characteristic withdrawal symptoms and dysregulated behaviors of the central and autonomic nervous systems commonly attributed to neonatal abstinence syndrome/neonatal opioid withdrawal syndrome.[1-3] While first-line strategies are typically sufficient to manage the care of infants with mild symptoms,[4-7] pharmacotherapy is used to treat infants for whom first-line strategies are inadequate.[8-10] Pharmacologic agents used to treat newborns with POE include federally controlled opioid agonists (eg, morphine, methadone) and other prescribed medications (eg, phenobarbital) with known adverse effects on development.[11-20] Alternative nonpharmacologic interventions are critically needed for hospitalized newborns with POE to reduce the consequences of in utero exposures that may be further exacerbated by postnatal pharmacologic treatment.

A growing amount of research suggests the importance of tactile sensory stimulation for promoting physiologic maturation and brain development, and for improving behaviors implicated in intrauterine drug exposure.[21-34] Evidence supports that stochastic (ie, random, noisy) mechanostimulation can promote stability in destabilized biological systems.[35-39] In preliminary studies by some of the authors of the present study, low-level stochastic vibrotactile stimulation (SVS) delivered through a uniquely constructed crib mattress improved physiologic function in newborns with neonatal abstinence syndrome.[40,41]

A main objective of this trial was to test the therapeutic efficacy of SVS for reducing pharmacologic treatment in newborns with POE hospitalized since birth.[42] We hypothesized that daily administration of SVS complementary to standard care would reduce the severity of withdrawal symptoms and dysregulated behaviors, resulting in less pharmacotherapy throughout the infant's hospitalization. Morphine treatment was compared between newborns with POE randomized to receive SVS or treatment as usual (TAU).

Key Points

Question Is stochastic vibrotactile stimulation (SVS) via a crib mattress an effective intervention for reducing pharmacologic treatment in newborns with prenatal opioid exposure (POE)?

Findings In this randomized clinical trial, analysis of 181 newborns with POE revealed SVS duration was associated with a significantly reduced risk of pharmacologic treatment. Among infants who completed pharmacotherapy within 3 weeks, those receiving SVS completed treatment in 3.18 fewer days and received 1.76 mg/kg less morphine than infants treated as usual.

Meaning The findings of this study suggest that SVS may serve as a complementary nonpharmacologic intervention for treating infants with POE; less pharmacotherapy has implications for reduced hospitalization and costs.

Methods

Study Design

Reporting and analysis for this trial followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline; the trial protocol is available in Supplement 1.[42] The University of Massachusetts (UMass) Medical School Institutional Review Board approved the study through a reliance agreement with the University of Pittsburgh (UPitt). Participants were recruited at UMass between March 9, 2017, and February 25, 2020, and at UPitt between August 18, 2017, and March 10, 2020. The in-hospital bedside studies were conducted in neonatal units where infants received around-the-clock medical care. Written informed consent was obtained from the biological mother of each infant either prenatally or within 48 hours after delivery.

This prospective dual-site randomized clinical parallel group modified (analyzed for condition received) intention-to-treat trial evaluated the therapeutic efficacy of SVS for reducing pharmacologic treatment in term (≥37 weeks' gestation) newborns with POE. Randomization (TAU or SVS) used a computer-generated force-block design to ensure even allocation of the intervention for each site and birth sex. The design, hypotheses, sample size, and power calculations were created before availability of the trial results (Supplement 1).[42]

Inclusion and Exclusion Criteria

Eligible infants were newborns at greater than or equal to 37 weeks' gestation with POE (confirmed meconium and/or urine toxicology report and/or documented in utero opioid exposure, such as methadone, buprenorphine, oxycodone, and heroin) receiving neonatal care at UMass or UPitt.[42] Exclusion criteria included clinically significant congenital anomalies, hydrocephalus, intracranial hemorrhage greater than grade 2, seizures not related to drug withdrawal, anemia (hemoglobin <8.0 g/dL [to convert to grams per liter, multiply by 10]), hypoxic ischemia encephalopathy, respiratory failure requiring invasive ventilatory support, or receiving treatment for bacterial or viral conditions.

Protocol

Enrollment and randomization to TAU or SVS occurred within 48 hours of birth in the newborn unit. Infants assigned to SVS had their hospital crib mattress replaced with a uniquely constructed SVS study mattress (30-60 Hz, approximately 12 µm root mean square; Wyss Institute, Harvard University; Cofab Design, LLC)[42,43] with a preprogrammed, 3-hour SVS on-off cycle continuously. The SVS cycled on and off even if the infant was not in their crib.

Per standard of care, all infants received nonpharmacologic strategies[4-7] and were assessed clinically for signs and symptoms of withdrawal via the modified Finnegan tool.[44,45] Infants who developed symptom severity that met clinical criteria for pharmacologic treatment based on common conventional clinical protocol[46] (ie, 3 consecutive Finnegan scores ≥8 or 2 consecutive scores ≥12) determined by the infant's medical care team were transferred to the neonatal intensive care unit (NICU) for treatment. As a safety protocol for infants assigned SVS whose symptoms did not meet the criteria for treatment during the newborn unit observation period, the SVS mattress was turned off 12 to 24 hours before the anticipated

discharge from the hospital to allow for observation of the infant without SVS. If an infant exhibited signs of withdrawal that met clinical criteria to treat, the infant was transferred to the NICU per standard of care and the SVS intervention was resumed. For all infants transferred to the NICU for pharmacotherapy, SVS was shut off on completion of morphine treatment (ie, first-line medication) regardless of the continuation of other treatment medications. Start/stop times of the mattress cycle varied by initial enrollment time, newborn observation, and NICU treatment periods. The SVS start/stop times, cycle periods, and deviations (eg, stops/restarts due to technical issues, safety protocol, or parental/medical requests) were noted in a date- and time-stamped computerized bedside study log. Infants randomized to TAU received only the standard hospital-issued nonoscillating crib mattress throughout hospitalization.

All infants received site standard of care and caregivers were instructed to provide care as they typically would, including feeding, holding, and using hospital-issued motorized seats (mamaRoo; 4moms). Caregivers were further instructed to log bedside activities, providing a 24-hour record of infant time in the crib vs being held or in a motorized seat. The study log also indicated when the infants assigned SVS were in the crib with and without stimulation.

Infant and maternal demographic characteristics and medical history, and infant daily clinical assessments throughout hospitalization (eg, Finnegan scores, pharmacologic treatment, and feeds) were obtained from electronic medical records and maternal questionnaires. Race and ethnicity were obtained per National Institutes of Health reporting requirements and to assess associations with outcomes. Race and ethnicity were reported by the biological mother from a questionnaire with predefined categories. Data were entered into the study database (REDCap).[47,48]

Outcomes

The a priori primary outcomes analyzed for this article were pharmacotherapy and hospital duration (Supplement 1). The primary end points for pharmacotherapy were administration of morphine treatment (AMT), the first-line medication at both sites (number of infants treated), and the cumulative morphine dose (CMD) (the sum of the ratio of daily milligrams of morphine per kilogram body weight). The primary end point for hospital duration was length of stay (days). Because length of stay was affected by factors unrelated to medical condition and care, such as delays in discharge due to guardianship and housing, the associated outcome that focused on length of morphine treatment (LOT) (the number of days receiving morphine) was also analyzed.

This is a new device and given the lack of interventional device studies when the trial was designed, we examined the influence of pertinent variables identified a priori (eg, demographic data, prenatal drug exposure, and postnatal feed type) (Supplement 1).[42] Because infants were studied at the bedside to support routine care, impartial to condition assignment, SVS assignment did not guarantee an infant would be in the crib when the stimulation was on. Thus, we also analyzed dose-response effects of bedside activities on the primary outcomes: duration (hours per day) that the infant received SVS on, SVS off, caregiver hold, and hospital-issued motorized seats.

Sample Size Calculation

In the original development of the study, we used Finnegan score to estimate sample size (Supplement 1). Given emerging concerns on the meaningfulness of the Finnegan score as a primary outcome,[45,49] we focused analyses on pharmacotherapy (AMT, CMD, and LOT) and hospitalization duration (length of stay). We did not recalculate the sample size post hoc; calculations reported in other studies[8,50] indicated our study sample size was adequate to detect differences (Supplement 1).

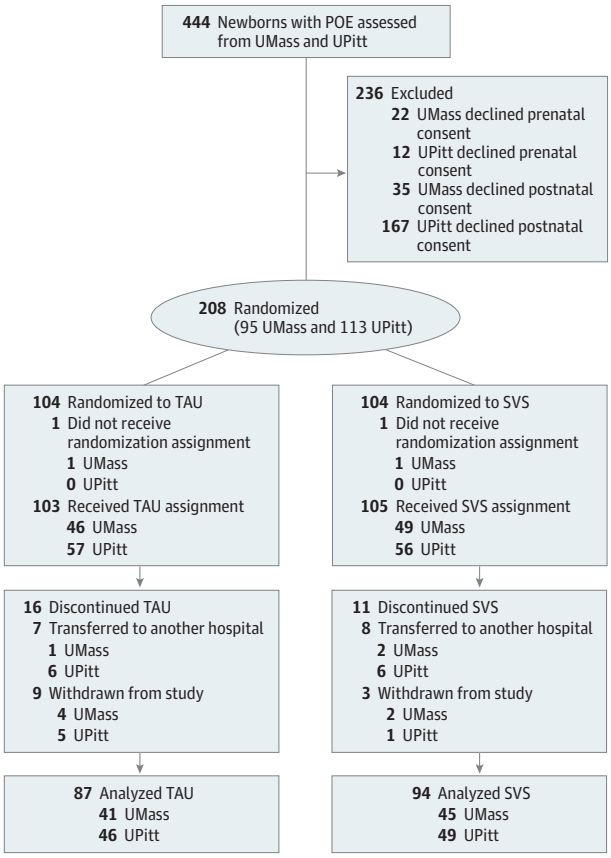
Statistical Analysis

Demographic and other baseline mother and infant characteristics were described by condition (TAU or SVS). Unadjusted effects of SVS condition on each primary outcome were compared using 2-sample *t* tests. Adjusted effects of SVS condition and daily duration were assessed using regression-based models. Associations of dose-response variables with each outcome were also analyzed. The AMT was analyzed with an adjusted logistic regression model using the population of infants who completed hospitalization; CMD and LOT were analyzed using the cohort of infants who received pharmacologic treatment in the NICU. Cumulative morphine dose was analyzed with multiple linear regression. Analyses of LOT were performed using a negative binomial regression model. Given the novelty of the device, for exploratory purposes for future studies, all models were adjusted for possible factors that could influence treatment outcomes as identified a priori in the protocol (ie, site, type of opioid the infant was exposed to in utero, whether the infant was receiving breast milk at day of discharge, birth weight, and sex). All statistical analyses were performed using R programming, version 1.4.1717 (R Foundation for Statistical Computing). Cox proportional hazards models were analyzed using the survival library. Kaplan-Meier and forest plot curves were plotted using the ggplot2 library. Analyses were performed according to condition received, noting that 1 infant assigned to TAU received SVS due to staff allocation error. Statistical significance was determined with a threshold level of $\alpha = .05$. All adjusted analyses are presented with 95% CIs.

Results

A total of 208 mother/infant dyads were enrolled (**Figure 1**; eTable 1 in Supplement 2); 104 infants were randomized to TAU and 104 to the mattress SVS intervention. Analyses were performed on 181 infants who completed hospitalization at their study site (mean [SD] birth gestational age, 39.0 [1.2] weeks; mean [SD] birth weight, 3076 [489] g; 100 [55.2%] were female; 81 [44.8%] were male; for race, 5 [2.8%] were Black or African American; 1 [0.6%] Native Hawaiian or Other Pacific Islander; 29 [16.0%] multiracial; 138 [76.2%] White; 8 [4.4%] unknown; for ethnicity, 18 [9.9%] Hispanic or Latino; 155

Figure 1. Flow Diagram of Participant Enrollment



SVS indicates stochastic vibrotactile stimulation (intervention); TAU, treatment as usual (control); UMass, University of Massachusetts; and UPitt, University of Pittsburgh.

[85.5%] Non-Hispanic or Latino; 8 [4.4%] unknown; 87 TAU [48.1%]; and 94 SVS [51.9%; includes the infant assigned to TAU who received SVS]). Demographic variables and other characteristics were similar between groups (**Table 1** [analyzed cohort]; eTable 2 in Supplement 2 [full cohort]), except in the analyzed cohort there were more infants exposed to opioids (illicit or prescribed) not specified for medication-assisted therapy in the SVS group (9.6%) than the TAU group (1.1%) (P = .03). Of the 27 infants who did not complete hospitalization, 14 were withdrawn from the study and 13 were transferred to another hospital (eTable 1 in Supplement 2).

Unadjusted comparisons of outcomes are provided in **Table 2**. Of the 181 analyzed infants, 121 (66.9%) were discharged without medication and 60 (33.1%) were transferred to the NICU for morphine treatment (31 [51.7%] TAU and 29 [48.3%] SVS). Treatment rate was 5% higher in the TAU group (31 of 87 infants [35.6%]) than the SVS group (29 of 94 infants [30.9%]) but this difference was not statistically significant (P = .60). Day of life the infants started treatment was not significantly different between the TAU and SVS groups (Table 2). Among the untreated infants, there was no significant difference in day of life at which the infants were discharged from the newborn unit between the TAU (mean [SD], 5.7 [1.3] days) and SVS (mean [SD], 5.9 [1.6] days) groups (P = .55). Of note, per study safety protocol, among the full cohort of 105 infants who received SVS there were 58 infants in whom SVS was turned off in the newborn unit 12 to 24 hours before the anticipated discharge for infant observation. Within 24 hours of shutting off SVS, 6 infants (10.3%) met the criteria for pharmacotherapy and were transferred to the NICU for treatment.

Adjusted analyses of AMT with dose-response variables for the analyzed group (n = 181) revealed that SVS duration in the newborn unit (hours per day) was associated with a reduction in AMT (odds ratio [OR], 0.88 hours per day; 95% CI, 0.81-0.93 hours per day) (**Table 3**). This corresponded to a 50% reduction in AMT for infants receiving SVS, on average, 6 hours per day in the newborn unit. Adjusting for the duration of each of the bedside activities, the amount of time infants were held by caregivers in the newborn unit was also associated with a reduced AMT (OR, 0.90 hours per day; 95% CI, 0.86-0.94 hours per day) (Table 3). Post hoc analyses showed that the effects of SVS duration (OR, 0.89 hours per day; 95% CI, 0.89-0.95 hours per day) and caregiver hold time (OR, 0.91 hours per day; 95% CI, 0.86-0.95 hours per day) on AMT were additive when considered jointly in the regression model.

Infants Treated With Morphine

Adjusted analyses of the 60 infants who were transferred to the NICU and received morphine treatment revealed no significant differences in CMD or LOT between the 2 conditions (Table 3). However, it was evident from the Kaplan-Meier plot (**Figure 2**) that among infants who completed treatment within 3 weeks (responders), LOT differed between infants who received SVS vs TAU; 58.6% (17 of 29) of infants who received SVS finished treatment within 3 weeks compared with 48.4% (15 of 31) of infants who received TAU. Analyses revealed that, within this time period, infants who received SVS finished treatment nearly twice as fast (hazard ratio, 1.96; 95% CI, 1.01-3.81), resulting in a 26% decrease in LOT or 3.18 fewer treatment days than infants who received TAU (95% CI, −0.47 to −0.04) (eTable 3 in Supplement 2). Adjusted analyses of this responder group also revealed that the mean CMD was 1.76 mg/kg less for infants who received SVS vs TAU (95% CI, −3.02 to −0.50) (eTable 3 in Supplement 2). For infants treated for more than 21 days (nonresponders), there was no significant difference between conditions for CMD or LOT (eTable 4 in Supplement 2). As noted in Table 2, there were significantly more nonresponders (67.9%) who received adjunctive phenobarbital than responders (3.1%) (P < .001).

Prenatal opioid exposure to methadone (maternal medication-assisted therapy) played a significant role in AMT, CMD, and LOT in adjusted analyses controlling for condition and a priori cofactors: infants with prenatal methadone exposure had a higher rate of AMT (OR, 2.30; 95% CI, 1.15-4.62) (Table 3), and responders with prenatal methadone exposure had higher a CMD mean (2.48 mg/kg; 95% CI, 1.14-3.82 mg/kg) and longer LOT (mean change, 0.36; 95% CI, 0.01-0.59) than infants of mothers receiving buprenorphine therapy (eTable 3 in Supplement 2). There were no interactions between methadone exposure and condition. Increases in CMD and LOT were observed among responders with methadone exposure for all 5

Table 1. Infant and Maternal Demographic Characteristics for Cohorts Who Completed Hospitalization at Study Site[a]

Characteristic	Analyzed cohort (n = 181)		Treated cohort (n = 60)		Responder cohort (n = 32)	
	TAU	SVS	TAU	SVS	TAU	SVS
Infant characteristics						
Total No. (%)	87 (48.1)	94 (51.9)[b]	31 (51.7)	29 (48.3)	15 (46.9)	17 (53.1)
Sex, No. (%)						
Male	40 (46.0)	41 (43.6)	13 (41.9)	11 (37.9)	7 (46.7)	6 (35.3)
Female	47 (54.0)	53 (56.4)	18 (58.1)	18 (62.1)	8 (53.3)	11 (64.7)
Race,[c] No. (%)						
Black or African American	2 (2.3)	3 (3.2)	1 (3.2)	1 (3.4)	0	1 (5.9)
Native Hawaiian or Other Pacific Islander	0	1 (1.1)	0	0	0	0
White	68 (78.2)	70 (74.5)	23 (74.2)	22 (75.9)	12 (80.0)	12 (70.6)
Multiracial	14 (16.1)	15 (16.0)	4 (12.9)	5 (17.2)	2 (13.3)	4 (23.5)
Unknown	3 (3.5)	5 (5.3)	3 (9.7)	1 (3.5)	10 (6.7)	0
Ethnicity,[c] No. (%)						
Hispanic	9 (10.3)	9 (9.6)	4 (12.9)	3 (10.3)	1 (6.7)	0
Non-Hispanic	74 (85.1)	81 (86.2)	24 (77.4)	26 (89.7)	13 (86.7)	17 (100)
Unknown	4 (4.6)	4 (4.3)	3 (9.7)	0	1 (6.7)	0
Enrolled at UMass, No. (%)	41 (47.1)	45 (47.9)	17 (54.8)	17 (58.6)	4 (26.7)	7 (41.2)
Enrolled at UPitt, No. (%)	46 (52.9)	49 (52.1)	14 (45.2)	12 (41.4)	11 (73.3)	10 (58.8)
Gestational age, mean (SD), wk	39.1 (1.2)	38.9 (1.2)	39.2 (1.2)	38.9 (1.1)	38.9 (1.2)	38.8 (1.1)
Birth weight, mean (SD), g	3086 (454)	3066 (520)	3092 (483)	2993 (410)	3110 (503)	2966 (421)
Birth head circumference, mean (SD), cm	33.6 (1.9)	33.4 (1.7)	33.3 (1.6)	33.3 (1.4)	33.5 (1.2)	33.4 (1.5)
Apgar score 1 min, mean (range)	8.0 (4-9)	7.9 (1-10)	7.7 (4-9)	8.2 (5-9)	7.9 (5-9)	8.3 (7-9)
Apgar score 5 min, mean (range)	8.8 (6-9)	8.8 (6-10)	8.8 (8-9)	8.9 (8-10)	8.9 (8-9)	8.9 (8-9)
Cesarean delivery, No. (%)	20 (23.0)	20 (21.3)	5 (16.1)	5 (17.2)	4 (26.7)	3 (17.6)
Formula-fed only, No. (%)	31 (35.6)	34 (36.2)	12 (38.7)	10 (34.5)	7 (46.7)	5 (29.4)
Discharged receiving breast milk, No. (%)	42 (48.3)	49 (52.1)	13 (41.9)	11 (37.9)	7 (46.7)	7 (41.2)
Biological mother						
Maternal age at infant's birth, mean (SD), y	30.7 (5.3)	29.3 (4.7)	30.9 (4.7)	28.6 (4.0)	29.7 (3.9)	28.3 (4.1)
MAT buprenorphine, No. (%)	52 (59.8)	51 (54.3)	15 (48.4)	10 (34.5)	10 (66.7)	6 (35.3)
MAT methadone, No. (%)	34 (39.1)	34 (36.2)	16 (51.6)	15 (51.7)	5 (33.3)	8 (47.1)
Non-MAT opioid, No. (%)	1 (1.1)	9 (9.6)	0	4 (13.8)	0	3 (17.6)

Abbreviations: MAT, medication-assisted therapy; SVS, stochastic vibrotactile stimulation; TAU, treatment as usual; UMass, University of Massachusetts; UPitt, University of Pittsburgh.

[a] Analyzed cohort comprised infants who completed hospitalization; treated cohort, a subset of the analyzed cohort who received morphine treatment; and responder cohort, a subset of the treated cohort who completed morphine treatment in 21 days or less.

[b] Included 1 infant assigned to TAU but received SVS.

[c] Race and ethnicity were reported by the biological mother from a questionnaire with predefined categories: Black or African American, Hispanic or Latino, Native Hawaiian or Other Pacific Islander, and White.

duration variables. Among responders, site differences were also observed: CMD and LOT were reduced at UPitt for 4 duration variables (eTable 3 in Supplement 2). Among nonresponders, site differences in LOT were increased at UMass for 4 duration variables (eTable 4 in Supplement 2). Notably, UMass had 1.8 times more infants exposed to methadone than UPitt. The Finnegan score range throughout hospitalization was similar between sites: UMass range, 0 to 21 (median, 5; IQR, 4-6); UPitt range, 0-19 (median, 6; IQR, 4-8).

Discussion

There is a critical clinical need for nonpharmacologic interventions to treat newborns with POE. Reports indicate that, on average, 70% of newborns with POE receive pharmacotherapy,[51] despite evidence that common-use treatment opioids and other pharmacotherapies impact infant behavior and develop- ment.[11,13,17,20] To our knowledge, this dual-site study is the first randomized clinical trial to examine the efficacy of SVS as a nonpharmacologic intervention for treating newborns with POE. A key finding was that daily duration of SVS reduced the likelihood an infant would be treated with morphine (OR, 0.88 hours per day; 95% CI, 0.81-0.93 hours per day), equivalent to a 50% reduction in AMT among infants who received SVS, on average, 6 hours per day while in the newborn unit. Furthermore, among infants with pharmacologically managed care who completed morphine treatment within 3 weeks, those receiving SVS had 3.18 fewer treatment days and 1.76 mg/kg less CMD than those assigned to TAU. Together, these findings support the efficacy of SVS for reducing medication treatment in newborns with POE, which has implica-

Table 2. Unadjusted Comparisons of Outcomes[a]

Outcome	Analyzed cohort (n = 181)		Treated cohort (n = 60)		Responders (n = 32)		Nonresponders (n = 28)	
	TAU	SVS	TAU	SVS	TAU	SVS	TAU	SVS
Administration of morphine treatment, No. (% within condition)	31 (35.6)	29 (30.9)	31 (100)	29 (100)	15 (100)	17 (100)	16 (100)	12 (100)
Day of life started treatment, mean (SD), d	NA	NA	2.94 (1.75)	2.48 (1.21)	3.27 (1.58)	2.71 (1.10)	2.63 (1.89)	2.17 (1.34)
Length of treatment, median (IQR), d	NA	NA	21 (17-25)	17 (12-25)	17 (12-19)	13 (8-16)	25 (22-29)	26 (24-34)
Cumulative morphine dose, mean (SD), mg/kg	NA	NA	8.22 (7.47)	7.31 (6.57)	4.33 (2.77)	3.21 (1.50)	11.87 (8.67)	13.14 (6.58)
Administered phenobarbital, No. (%)	9 (10.3)	11 (11.7)	9 (29.0)	11 (37.9)	0	1 (5.8)	9 (56.2)	10 (83.3)
Administered clonidine, No. (%)	1 (1.1)	0	1 (3.2)	0	0	0	1 (6.3)	0
Length of stay, median (IQR), d	7 (5-21)	6 (5-13)	26 (19-30)	21 (15-29)	18 (16-24)	17 (13-20)	29 (27-33)	30 (29-37)

Abbreviations: SVS, stochastic vibrotactile stimulation; TAU, treatment as usual.

[a] Analyzed cohort comprised infants who completed hospitalization; treated cohort, subset of analyzed cohort who received morphine treatment; responders, subset of treated cohort who completed morphine treatment in 21 days or less; and nonresponders, subset of treated cohort who completed morphine treatment in more than 21 days.

tions for improved neurodevelopmental outcomes, as well as associated hospitalization stays, subsequent cares, and care costs.[51,52]

Caregiver holding time also reduced the likelihood of AMT (OR, 0.90 hours per day; 95% CI, 0.86-0.94 hours per day), and was equivalent to that observed with SVS. In contrast, duration in standard of care hospital-issued motorized seats had no effect on AMT. The more tactile stimulation, either by gentle SVS vibration or caregiver hold, the lower the likelihood of pharmacologic treatment. These findings support the importance of mechanosensory stimulation for reducing withdrawal symptoms and promoting regulated systems.[21,28,32,40] While there is no replacement for natural touch by a caregiver to an infant, given that caregivers are not always available to hold infants in the hospital setting, SVS may provide a beneficial intervention to promote health equity and improve clinical outcomes among vulnerable newborns with POE.

A strength of this study was that a safety protocol was included for infants who received SVS whose symptoms did not meet the criteria for treatment while in the newborn unit: SVS was shut off 12 to 24 hours before the anticipated discharge. Within this safety-observation period, 10% of infants who received SVS met symptom criteria and were transferred to the NICU for morphine treatment. These findings exemplify the importance of adequate observation periods to safeguard that infants are not discharged under the misconception that symptoms have resolved and reduce the likelihood of readmission and other adverse consequences.[51-54] Symptoms remained below the criteria for treatment in a large subset of infants who received SVS and 10% of infants met treatment criteria during the safety observation after SVS was shut off, supporting that SVS may mitigate symptoms and serve as a nonpharmacologic intervention for treating newborns with POE.

Approximately 33% of the analyzed cohort received pharmacologic treatment, which is on the lower end of the national average (mean, 65%; range, 13%-90%).[51] Even though few infants met the criteria for treatment (n = 60), significant effects were observed, particularly among infants who completed treatment within 3 weeks; the longer infants received SVS in the newborn unit, the shorter the treatment and the less cumulative dose of morphine. Among infants who did not respond readily to pharmacotherapy (eg, treatment >21 days), there was no noticeable effect of SVS on LOT or CMD. Notably, 68% of nonresponders received adjunctive medications compared with 3% of responders. We speculate that infants whose dysregulation is due to withdrawal will respond to morphine and/or SVS, whereas dysregulation in nonresponders may reflect in utero development disruptions, polydrug exposure, and other teratogens that may require alternative modes of treatment.[3,40,55,56] It will be important for future studies to identify subgroups who may be more responsive to SVS.

Independent of condition, methadone exposure and study site played a major role in morphine treatment. Findings that methadone increased the likelihood of AMT, LOT, and CMD are consistent with research comparing methadone and buprenorphine.[57] Site differences may partially be explained by differences in medication-assisted therapy exposure (UPitt had more infants receiving buprenorphine, UMass had more infants receiving methadone), and by the UPitt Parent Partnership Unit,[58] a program implemented midway through the study in the UPitt newborn unit wherein mothers cared for their newborns in a private room throughout the postpartum observational period. Infants who met the criteria for treatment were transferred to the NICU and received pharmacotherapy per standard of care. A total of 40 UPitt study infants participated in the UPitt Parent Partnership Unit program (19 TAU and 21 SVS); none received pharmacotherapy. Finnegan scoring also likely did not contribute to site differences, as the score range was comparable between sites.

Limitations

The trial has limitations. It was intricate and had practical limitations as we prioritized routine care and conducted the study at the bedside in the newborns' hospital setting, monitoring the infant continuously whether they were in the newborn unit's nursery, with mother/family in a private room, in the

Table 3. Adjusted Pharmacologic Outcomes

Outcome variable and factor	Model				
	Condition (0 = TAU)	Time SVS on (h/d)	Time SVS off (h/d)	Time held (h/d)	Time in motorized seat (h/d)
AMT (n = 181)[a]					
Main effect	0.74 (0.37 to 1.44)	0.88 (0.81 to 0.93)[b]	0.99 (0.97 to 1.00)	0.90 (0.86 to 0.94)[b]	0.99 (0.97 to 1.01)
Site (0 = UMass)	0.60 (0.31 to 1.18)	0.25 (0.08 to 0.72)[b]	0.66 (0.32 to 1.32)	0.71 (0.33 to 1.54)	0.72 (0.36 to 1.43)
Sex (0 = female)	0.78 (0.40 to 1.52)	0.68 (0.29 to 1.59)	0.82 (0.41 to 1.62)	0.82 (0.38 to 1.75)	0.78 (0.39 to 1.54)
Birth weight	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.00)	1.00 (0.99 to 1.00)	1.00 0.99 to 1.00)	1.00 (0.99 to 1.00)
Methadone exposure (0 = buprenorphine)	2.30 (1.15 to 4.62)[b]	1.46 (0.59 to 3.60)	1.99 (0.98 to 4.06)	1.86 (0.85 to 4.10)	2.12 (1.05 to 4.32)[b]
Non-MAT exposure (0 = buprenorphine)[c]	2.43 (0.52 to 10.87)	2.24 (0.26 to 15.17)	0.91 (0.12 to 4.76)	1.16 (0.15 to 6.67)	1.13 (0.15 to 5.79)
Breast milk at discharge (0 = no)	0.52 (0.26 to 1.00)	0.64 (0.27 to 1.50)	0.53 (0.26 to 1.06)	0.64 (0.30 to 1.36)	0.57 (0.28 to 1.12)
CMD (n = 60)[d]					
Main effect	−1.08 (−4.77 to 2.61)	−0.24 (−0.56 to 0.08)	−0.02 (−0.06 to 0.03)	−0.19 (−0.37 to 0.00)	−0.05 (−0.14 to 0.05)
Site (0 = UMass)	−4.33 (−8.03 to −0.64)[b]	−2.60 (−6.54 to 1.34)	−3.67 (−7.66 to 0.32)	−3.84 (−7.62 to −0.06)[b]	−3.40 (−7.44 to 0.65)
Sex (0 = female)	−0.80 (−4.43 to 2.83)	−0.48 (−4.29 to 3.33)	−1.25 (−5.20 to 2.70)	−1.09 (−4.88 to 2.69)	−1.42 (−5.32 to 2.48)
Birth weight	0.00 (0.00 to 0.01)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)
Methadone exposure (0 = buprenorphine)	2.82 (−1.08 to 6.73)	4.20 (0.44 to 7.95)[b]	1.96 (−2.18 to 6.10)	1.67 (−2.33 to 5.67)	2.42 (−1.77 to 6.61)
Non-MAT exposure (0 = buprenorphine)[c]	−0.48 (−8.23 to 7.26)	−1.85 (−9.76 to 6.05)	−4.80 (−14.99 to 5.39)	−4.27 (−14.07 to 5.53)	−4.68 (−14.81 to 5.44)
Breast milk at discharge (0 = no)	−2.98 (−6.64 to 0.67)	−0.58 (−4.19 to 3.02)	−2.24 (−6.14 to 1.67)	−2.81 (−6.62 to 1.00)	−2.52 (−6.47 to 1.42)
LOT (n = 60)[e]					
Main effect	−0.07 (−3.31 to 0.18)	−0.03 (−0.06 to 0.01)	0.00 (0.00 to 0.00)	−0.01 (−0.03 to 0.00)	0.00 (−0.01 to 0.00)
Site (0 = UMass)	−0.36 (−0.62 to −0.11)[b]	−0.31 (−0.69 to 0.07)	−0.30 (−0.57 to −0.03)[b]	−0.33 (−0.59 to −0.07)[b]	−0.29 (−0.56 to −0.01)[b]
Sex (0 = female)	0.00 (−0.26 to 0.25)	−0.05 (−0.42 to 0.32)	−0.07 (−0.34 to 0.20)	−0.04 (−0.30 to 0.21)	−0.08 (−0.35 to 0.18)
Birth weight	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)
Methadone exposure (0 = buprenorphine)	0.28 (0.01 to 0.56)[b]	0.37 (0.01 to 0.74)[b]	0.24 (−0.05 to 0.52)	0.22 (−0.05 to 0.50)	0.27 (−0.01 to 0.56)
Non-MAT exposure (0 = buprenorphine)[c]	−0.11 (−0.66 to 0.43)	−0.62 (−1.47 to 0.24)	−0.83 (−1.63 to −0.04)[b]	−0.77 (−1.54 to 0.00)	−0.82 (−1.61 to −0.03)[b]
Breast milk at discharge (0 = N)	−0.17 (−0.43 to 0.08)	−0.03 (−0.38 to 0.32)	−0.11 (−0.38 to 0.16)	−0.15 (−0.41 to 0.11)	−0.13 (−0.40 to 0.14)

Abbreviations: AMT, administration of morphine treatment for the analyzed cohort; CMD, cumulative morphine dose for the treated cohort; LOT, length of treatment for the treated cohort; MAT, medication-assisted therapy; SVS, stochastic vibrotactile stimulation; TAU, treatment as usual.

[a] Odds ratio (95% CI) of AMT for each covariate of the estimated logistic regression models.

[b] Significant effects at 95% CI.

[c] In utero opioid exposure not prescribed for maternal treatment for opioid-use disorder (eg, prescribed oxycodone, illicit heroin).

[d] Mean (95% CI) change in CMD for unit increase of each covariate of the estimated linear regression models.

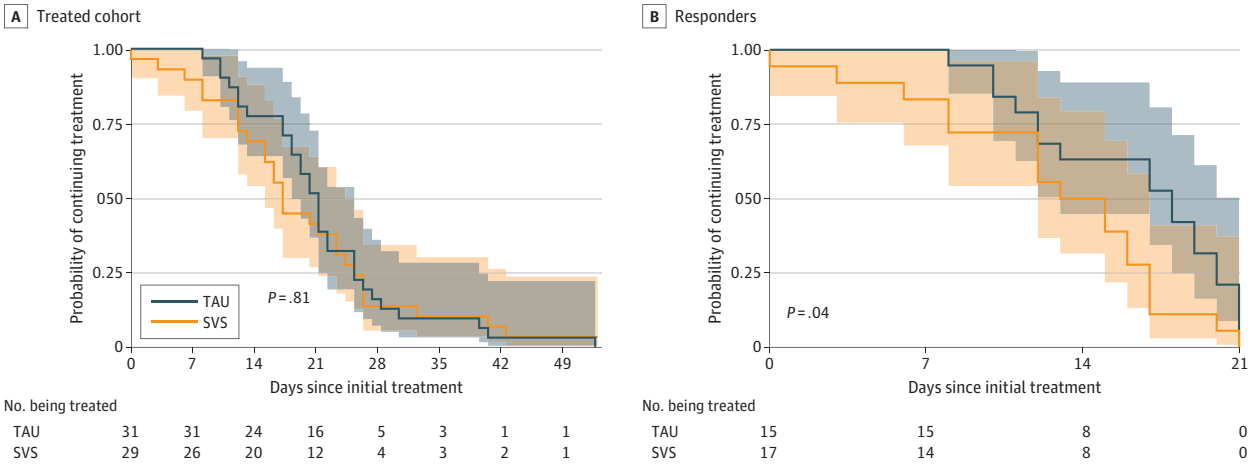
[e] Mean percentage (95% CI) change in LOT for unit increase of each covariate of the estimated negative binomial models.

NICU open pod, or when wheeled between locales. A particular limitation was our reliance on computer log reports by caregivers (medical, family, and research) at the bedside as to when the infant was in the crib, which we assumed to be of comparable reporting accuracy between the 2 conditions. There was concern for potential bias in caregiver assessments based on assignment given the inherent subjective limitations of the Finnegan tool,[45,59] the primary clinical measure that determined treatment regimens, and that caregivers could not be blinded to the SVS mattress given the nuances of the mattress device setup, including that the vibration from the mattress could be detected if touched. Anecdotal reports by caregivers suggest this is unlikely; for example, the bedside computer log for recording the infant's location was often misconstrued as the driver of stimulation, even among infants assigned to TAU. As well, findings that AMT was dependent on daily hours of SVS and was not simply a function of condition assignment suggests that caregiver assessments were not biased by unblinded allocation. In addition, we initiated SVS within 48 hours of birth, which is complementary to the standard of care including pharmacologic treatment. We did not test the effectiveness of SVS as an alternative to medication. Future studies are needed to identify optimal SVS periods and establish the effectiveness of SVS as a nonpharmacologic intervention alternative to pharmacotherapy based on conventional thresholds to treat.

Conclusions

In this randomized clinical trial, whole-body SVS with a crib mattress was associated with a reduced likelihood of mor-

Figure 2. Rate of Morphine Treatment Completion for Infants Receiving Treatment as Usual (TAU) and Stochastic Vibrotactile Stimulation (SVS)



A, Treated cohort. Of all infants who received morphine, there was no difference in rate of treatment completion between infants who received TAU and those who received SVS. B, Responders. Of infants who completed morphine treatment within 21 days, the rate of treatment completion was faster for infants who received SVS than those who received TAU. Note, 59% of infants who received SVS compared with 48% of those who received TAU completed treatment in 21 days or less. Shaded regions show the 95% CIs for the mean probability at each time point.

phine treatment in a cohort of newborns with POE. Moreover, among infants who were treated with morphine, SVS reduced LOT and CMD, particularly among treated infants who completed the morphine regimen within 3 weeks. The findings support the effectiveness of SVS as a complementary nonpharmacologic intervention for treating newborns with POE. Future studies are warranted to determine frequencies, durations, and timing to optimize the effect and ascertain the effectiveness of SVS as an alternative vs complementary treatment to pharmacotherapy.

ARTICLE INFORMATION

Accepted for Publication: March 9, 2023.

Published Online: May 15, 2023. doi:10.1001/jamapediatrics.2023.1077

Author Contributions: Drs Bloch-Salisbury and Wilson had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. In addition, Drs Bloch-Salisbury and Wilson contributed equally to writing the manuscript.
Concept and design: Bloch-Salisbury, Rodriguez, Beers, Bogen
Acquisition, analysis, or interpretation of data: Bloch-Salisbury, Wilson, Rodriguez, Bruch, McKenna, Derbin, Glidden, Ayturk, Aurora, Yanowitz, Barton, Vining, Beers, Bogen
Drafting of the manuscript: Bloch-Salisbury, Wilson
Critical revision of the manuscript for important intellectual content: Bloch-Salisbury, Wilson, Rodriguez, Bruch, McKenna, Derbin, Glidden, Ayturk, Aurora, Yanowitz, Barton, Vining, Beers, Bogen
Statistical analysis: Bloch-Salisbury, Wilson, Ayturk, Barton
Obtained funding: Bloch-Salisbury
Administrative, technical or material support: Bloch-Salisbury, Rodriguez, Bruch, McKenna, Derbin, Glidden, Aurora, Barton, Vining, Beers, Bogen
Supervision: Bloch-Salisbury, Yanowitz, Barton, Beers, Bogen

Conflict of Interest Disclosures: Dr Bloch-Salisbury reported holding a patent for PCT/US2015/ 021999 licensed to Prapela Inc. No other disclosures were reported.

Funding/Support: This trial was funded by the National Institute on Drug Abuse R01DA042074 (Bloch-Salisbury) and University of Massachusetts Research Trust Funds (Dr Bloch-Salisbury).

Role of the Funder/Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

Additional Contributions: James Niemi, MS, Hani Sallum, MS, and engineers at the Wyss Institute at Harvard University built the prototype mattresses and mattress calibration system. The Wyss Institute provided some mattresses and calibrations used for this trial. In collaboration with Messrs Niemi and Sallum, Mike Stone, BS, and engineers at Cofab Design LLC constructed study mattresses used in the trial, and Mark Gartner, PhD, and Jeff Speakman at the University of Pittsburgh Swanson School of Engineering constructed a mattress calibration system at the University of Pittsburgh site. Mr Niemi, Mr Sallum, and Kelsey Fafara, BS, at the Wyss Institute and Dr Gartner and Kevin Xu, BS, at the University of Pittsburgh provided routine calibrations to help ensure mattress integrity throughout the trial period. Dane Netherton, PhD, at the University of Massachusetts Medical School developed and maintained the REDCap program throughout the trial. Lidush Goldschmidt, PhD, at the University of Pittsburgh Medical Center provided statistical advice. We thank the nurses in the infant units at UMass Memorial Health Care and UPMC Magee-Women's Hospital for their logistical help, coordination, patience, and assistance implementing this intricate study into the routine care of the infants. No financial compensation outside of salary was provided for these services. We gratefully acknowledge the infants and families for participating in this clinical trial.

REFERENCES

1. Grossman M, Berkwitt A. Neonatal abstinence syndrome. *Semin Perinatol*. 2019;43(3):173-186. doi:10.1053/j.semperi.2019.01.007

2. Kocherlakota P. Neonatal abstinence syndrome. *Pediatrics*. 2014;134(2):e547-e561. doi:10.1542/peds.2013-3524

3. Velez ML, Jordan C, Jansson LM. Reconceptualizing non-pharmacologic approaches to neonatal abstinence syndrome (NAS) and neonatal opioid withdrawal syndrome (NOWS): a theoretical and evidence-based approach—part II: the clinical application of nonpharmacologic care for NAS/NOWS. *Neurotoxicol Teratol*. 2021;88:107032. doi:10.1016/j.ntt.2021.107032

4. McQueen KA. "Rooming-in" could be an effective non-pharmacological treatment for infants with neonatal abstinence syndrome. *Evid Based Nurs*. 2018;21(4):110. doi:10.1136/eb-2018-102948

5. Sublett J. Neonatal abstinence syndrome: therapeutic interventions. *MCN Am J Matern Child Nurs*. 2013;38(2):102-107. doi:10.1097/NMC.0b013e31826e978e

6. Velez M, Jansson LM. The opioid dependent mother and newborn dyad: non-pharmacologic

care. *J Addict Med*. 2008;2(3):113-120. doi:10.1097/ADM.0b013e31817e6105

7. Wachman EM, Schiff DM, Silverstein M. Neonatal abstinence syndrome advances in diagnosis and treatment. *JAMA*. 2018;319(13):1362-1374. doi:10.1001/jama.2018.2640

8. Davis JM, Shenberger J, Terrin N, et al. Comparison of safety and efficacy of methadone vs morphine for treatment of neonatal abstinence syndrome: a randomized clinical trial. *JAMA Pediatr*. 2018;172(8):741-748. doi:10.1001/jamapediatrics.2018.1307

9. Disher T, Gullickson C, Singh B, et al. Pharmacological treatments for neonatal abstinence syndrome: a systematic review and network meta-analysis. *JAMA Pediatr*. 2019;173(3):234-243. doi:10.1001/jamapediatrics.2018.5044

10. Hudak ML, Tan RC; Committee on Drugs; Committee on Fetus and Newborn; American Academy of Pediatrics. Neonatal drug withdrawal. *Pediatrics*. 2012;129(2):e540-e560. doi:10.1542/peds.2011-3212

11. Attarian S, Tran LC, Moore A, Stanton G, Meyer E, Moore RP. The neurodevelopmental impact of neonatal morphine administration. *Brain Sci*. 2014;4(2):321-334. doi:10.3390/brainsci4020321

12. Handelmann GE, Quirion R. Neonatal exposure to morphine increases mu opiate binding in the adult forebrain. *Eur J Pharmacol*. 1983;94(3-4):357-358. doi:10.1016/0014-2999(83)90429-6

13. de Graaf J, van Lingen RA, Simons SHP, et al. Long-term effects of routine morphine infusion in mechanically ventilated neonates on children's functioning: five-year follow-up of a randomized controlled trial. *Pain*. 2011;152(6):1391-1397. doi:10.1016/j.pain.2011.02.017

14. Handelmann GE, Dow-Edwards D. Modulation of brain development by morphine: effects on central motor systems and behavior. *Peptides*. 1985;6(suppl 2):29-34. doi:10.1016/0196-9781(85)90131-7

15. Juul SE, Beyer RP, Bammler TK, Farin FM, Gleason CA. Effects of neonatal stress and morphine on murine hippocampal gene expression. *Pediatr Res*. 2011;69(4):285-292. doi:10.1203/PDR.0b013e31820bd165

16. Le Marec T, Marie-Claire C, Noble F, Marie N. Chronic and intermittent morphine treatment differently regulates opioid and dopamine systems: a role in locomotor sensitization. *Psychopharmacology (Berl)*. 2011;216(2):297-303. doi:10.1007/s00213-011-2223-6

17. Menon G, Boyle EM, Bergqvist LL, McIntosh N, Barton BA, Anand KJ. Morphine analgesia and gastrointestinal morbidity in preterm infants: secondary results from the NEOPAIN trial. *Arch Dis Child Fetal Neonatal Ed*. 2008;93(5):F362-F367. doi:10.1136/adc.2007.119297

18. Pačesová D, Spišská V, Novotný J, Bendová Z. Maternal morphine intake during pregnancy and lactation affects the circadian clock of rat pups. *Brain Res Bull*. 2021;177:143-154. doi:10.1016/j.brainresbull.2021.09.016

19. Rozisky JR, Medeiros LF, Adachi LS, et al. Morphine exposure in early life increases nociceptive behavior in a rat formalin tonic pain model in adult life. *Brain Res*. 2011;1367:122-129. doi:10.1016/j.brainres.2010.10.041

20. Zwicker JG, Miller SP, Grunau RE, et al. Smaller cerebellar growth and poorer neruodevelopmental outcomes in very preterm infants exposed to morphine. *J Pediatr*. 2016;172:81-87.e2. doi:10.1016/j.jpeds.2015.12.024

21. Ardiel EL, Rankin CH. The importance of touch in development. *Paediatr Child Health*. 2010;15(3):153-156. doi:10.1093/pch/15.3.153

22. Bautista DM, Lumpkin EA. Perspectives on: information and coding in mammalian sensory physiology: probing mammalian touch transduction. *J Gen Physiol*. 2011;138(3):291-301. doi:10.1085/jgp.201110637

23. Carvell GE, Simons DJ. Abnormal tactile experience early in life disrupts active touch. *J Neurosci*. 1996;16(8):2750-2757. doi:10.1523/JNEUROSCI.16-08-02750.1996

24. Collins JJ, Imhoff TT, Grigg P. Noise-enhanced tactile sensation. *Nature*. 1996;383(6603):770. doi:10.1038/383770a0

25. Cramer SJE, Dekker J, Dankelman J, Pauws SC, Hooper SB, Te Pas AB. Effect of tactile stimulation on termination and prevention of apnea of prematurity: a systematic review. *Front Pediatr*. 2018;6:45. doi:10.3389/fped.2018.00045

26. Field T, Diego MA, Hernandez-Reif M, Deeds O, Figuereido B. Moderate versus light pressure massage therapy leads to greater weight gain in preterm infants. *Infant Behav Dev*. 2006;29(4):574-578. doi:10.1016/j.infbeh.2006.07.011

27. Field TM, Schanberg SM, Scafidi F, et al. Tactile/kinesthetic stimulation effects on preterm neonates. *Pediatrics*. 1986;77(5):654-658. doi:10.1542/peds.77.5.654

28. Heath A, Bainbridge N. *Baby Massage: The Calming Power of Touch*. D.K. Publishing, Inc; 2004.

29. Maruyama K, Shimoju R, Ohkubo M, Maruyama H, Kurosawa M. Tactile skin stimulation increases dopamine release in the nucleus accumbens in rats. *J Physiol Sci*. 2012;62(3):259-266. doi:10.1007/s12576-012-0205-z

30. Muhammad A, Hossain S, Pellis SM, Kolb B. Tactile stimulation during development attenuates amphetamine sensitization and structurally reorganizes prefrontal cortex and striatum in a sex-dependent manner. *Behav Neurosci*. 2011;125(2):161-174. doi:10.1037/a0022628

31. Muhammad A, Kolb B. Prenatal tactile stimulation attenuates drug-induced behavioral sensitization, modifies behavior, and alters brain architecture. *Brain Res*. 2011;1400:53-65. doi:10.1016/j.brainres.2011.05.038

32. Van Puyvelde M, Gorissen AS, Pattyn N, McGlone F. Does touch matter? the impact of stroking versus non-stroking maternal touch on cardio-respiratory processes in mothers and infants. *Physiol Behav*. 2019;207:55-63. doi:10.1016/j.physbeh.2019.04.024

33. Rana D, Garde K, Elabiad MT, Pourcyrous M. Whole body massage for newborns: a report on non-invasive methodology for neonatal opioid withdrawal syndrome. *J Neonatal Perinatal Med*. 2022;15(3):559-565. doi:10.3233/NPM-220989

34. White-Traut RC, Schwertz D, McFarlin B, Kogan J. Salivary cortisol and behavioral state responses of healthy newborn infants to tactile-only and multisensory interventions. *J Obstet Gynecol Neonatal Nurs*. 2009;38(1):22-34. doi:10.1111/j.1552-6909.2008.00307.x

35. Bloch-Salisbury E, Indic P, Bednarek F, Paydarfar D. Stabilizing immature breathing patterns of preterm infants using stochastic mechanosensory stimulation. *J Appl Physiol (1985)*. 2009;107(4):1017-1027. doi:10.1152/japplphysiol.00058.2009

36. Collins JJ, Imhoff TT, Grigg P. Noise-enhanced information transmission in rat SA1 cutaneous mechanoreceptors via aperiodic stochastic resonance. *J Neurophysiol*. 1996;76(1):642-645. doi:10.1152/jn.1996.76.1.642

37. Priplata AA, Niemi JB, Harry JD, Lipsitz LA, Collins JJ. Vibrating insoles and balance control in elderly people. *Lancet*. 2003;362(9390):1123-1124. doi:10.1016/S0140-6736(03)14470-4

38. Smith VC, Kelty-Stephen D, Qureshi Ahmad M, et al. Stochastic resonance effects on apnea, bradycardia, and oxygenation: a randomized controlled trial. *Pediatrics*. 2015;136(6):e1561-e1568. doi:10.1542/peds.2015-1334

39. Zeldich D, Bou Jawde S, Herrmann J, et al. Stabilizing breathing pattern using local mechanical vibrations: comparison of deterministic and stochastic stimulations in rodent models of apnea of prematurity. *Biomed Eng Lett*. 2021;11(4):383-392. doi:10.1007/s13534-021-00203-x

40. Bloch-Salisbury E, Rodriguez N, Bruch T, McKenna L, Goldschmidt L. Physiologic dysregulation in newborns with prenatal opioid exposure: cardiac, respiratory and movement activity. *Neurotoxicol Teratol*. 2022;92:107105. doi:10.1016/j.ntt.2022.107105

41. Zuzarte I, Indic P, Barton B, Paydarfar D, Bednarek F, Bloch-Salisbury E. Vibrotactile stimulation: a non-pharmacological intervention for opioid-exposed newborns. *PLoS One*. 2017;12(4):e0175981. doi:10.1371/journal.pone.0175981

42. Bloch-Salisbury E, Bogen D, Vining M, et al. Study design and rationale for a randomized controlled trial to assess effectiveness of stochastic vibrotactile mattress stimulation versus standard non-oscillating crib mattress for treating hospitalized opioid-exposed newborns. *Contemp Clin Trials Commun*. 2021;21:100737. doi:10.1016/j.conctc.2021.100737

43. Bloch-Salisbury E, Paydarfar D. Methods and systems for reducing irritability in infants. United States Patent Application Publication US 2017/0172411 A1. June 22, 2017. Accessed April 6, 2023. https://patentimages.storage.googleapis.com/2e/9b/e6/9df5be12e3552d/US20170172411A1.pdf

44. Finnegan LP. Neonatal abstinence syndrome: assessment and pharmacotherapy. In: Nelson N, ed. *Current Therapy in Neonatal-Perinatal Medicine*. 2nd ed. BC Decker; 1990.

45. Timpson W, Killoran C, Maranda L, Picarillo A, Bloch-Salisbury E. A quality improvement initiative to increase scoring consistency and accuracy of the Finnegan tool. *Adv Neonatal Care*. 2018;18(1):70-78. doi:10.1097/ANC.0000000000000441

46. Jansson LM, Velez M, Harrow C. The opioid-exposed newborn: assessment and pharmacologic management. *J Opioid Manag*. 2009;5(1):47-55. doi:10.5055/jom.2009.0006

47. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381. doi:10.1016/j.jbi.2008.08.010

48. Harris PA, Taylor R, Minor BL, et al; The REDCap consortium. Building an international community of software partners. *J Biomed Inform*. 2019;95. doi:10.1016/j.jbi.2019.103208

49. Schiff DM, Grossman MR. Beyond the Finnegan scoring system: novel assessment and diagnostic techniques for the opioid-exposed infant. *Semin Fetal Neonatal Med*. 2019;24(2):115-120. doi:10.1016/j.siny.2019.01.003

50. Zimmermann U, Rudin C, Duò A, Held L, Bucher HU; Swiss neonatal abstinence syndrome study group. Treatment of opioid withdrawal in neonates with morphine, phenobarbital, or chlorpromazine: a randomized double-blind trial. *Eur J Pediatr*. 2020;179(1):141-149. doi:10.1007/s00431-019-03486-6

51. Milliren CE, Gupta M, Graham DA, Melvin P, Jorina M, Ozonoff A. Hospital variation in neonatal abstinence syndrome incidence, treatment modalities, resource use, and costs across pediatric hospitals in the United States, 2013 to 2016. *Hosp Pediatr*. 2018;8(1):15-20. doi:10.1542/hpeds.2017-0077

52. Devlin LA, Lau T, Radmacher PG. Decreasing total medication exposure and length of stay while completing withdrawal for neonatal abstinence syndrome during the neonatal hospital stay. *Front Pediatr*. 2017;5:216. doi:10.3389/fped.2017.00216

53. Patrick SW, Burke JF, Biel TJ, Auger KA, Goyal NK, Cooper WO. Risk of hospital readmission among infants with neonatal abstinence syndrome. *Hosp Pediatr*. 2015;5(10):513-519. doi:10.1542/hpeds.2015-0024

54. Diop H, Cui X, Nielsen T, Peacock-Chambers E, Gupta M. Length of stay among infants with neonatal abstinence syndrome and risk of hospital readmission. *Matern Child Health J*. 2022;26(10):2020-2029. doi:10.1007/s10995-022-03481-8

55. Caritis SN, Panigrahy A. Opioids affect the fetal brain: reframing the detoxification debate. *Am J Obstet Gynecol*. 2019;221(6):602-608. doi:10.1016/j.ajog.2019.07.022

56. Nagaraj UD, Kline-Fath BM, Zhang B, et al. MRI findings in third-trimester opioid-exposed fetuses, with focus on brain measurements: a prospective multicenter case-control study. *AJR Am J Roentgenol*. 2023;220(3):418-427. doi:10.2214/AJR.22.28357

57. Tolia VN, Murthy K, Bennett MM, et al. Antenatal methadone vs buprenorphine exposure and length of hospital stay in infants admitted to the intensive care unit with neonatal abstinence syndrome. *J Perinatol*. 2018;38(1):75-79. doi:10.1038/jp.2017.157

58. The Parent Partnership Unit. UPMC Magee-Womens Hospital. Accessed October 23, 2022. https://www.upmc.com/locations/hospitals/magee/services/obstetrics-and-gynecology/obstetrics/magee-recovery-services/services/parent-partnership-unit

59. Jones HE, Seashore C, Johnson E, et al. Psychometric assessment of the neonatal abstinence scoring system and the MOTHER NAS scale. *Am J Addict*. 2016;25(5):370-373. doi:10.1111/ajad.12388