Neonatal Abstinence Syndrome Severity Index Predicts 18-Month Neurodevelopmental Outcome in Neonates Randomized to Morphine or Methadone

Tess Flannery, MPH[1], Jonathan M. Davis, MD[2,3,4], Adam J. Czynski, MD[5], Lynne M. Dansereau, MSPH[1], Erica L. Oliveira, BA[1], Samantha A. Camardo, BA[1], and Barry M. Lester, PhD[1,5,6]

Objective To develop an index to determine which opioid-exposed neonates have the most severe neonatal abstinence syndrome (NAS).

Study design Full-term neonates with NAS (n = 116) from mothers maintained on methadone or buprenorphine were enrolled from 8 sites into a randomized clinical trial of morphine vs methadone. Ninety-nine (85%) were evaluated at hospital discharge using the NICU Network Neurobehavioral Scale (NNNS). At 18 months, 83 of 99 (83.8%) were evaluated with the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III), and 77 of 99 (77.7%) were evaluated with the Child Behavior Checklist (CBCL).

Results Cluster analysis was used to define high (n = 21) and low (n = 77) NAS severity. Compared with infants in the low NAS severity cluster, infants in the high NAS severity cluster had a longer length of stay ($P < .001$), longer length of stay due to NAS ($P < .001$), longer duration of treatment due to NAS ($P < .001$), and higher total dose of the study drug ($P < .001$) and were more likely to have received phenobarbital ($P < .001$), to have been treated with morphine ($P = .020$), and to have an atypical NNNS profile ($P = .005$). The 2 groups did not differ in terms of maximum Finnegan score. At 18 months, in unadjusted analyses, compared with the high-severity cluster, the low-severity cluster had higher scores on the Bayley-III Cognitive ($P = .013$), Language ($P < .001$), and Motor ($P = .041$) composites and less total behavior problems on the CBCL ($P = .028$). In adjusted analyses, the difference in the Bayley-III Language composite remained ($P = .013$).

Conclusions Presumptive measures of NAS severity can be aggregated to develop an index that predicts developmental outcomes at age 18 months. *(J Pediatr 2020;227:101-7)*.

The number of neonates exposed to opioids in utero in the US has increased by 333% in the past 2 decades, which translates to approximately 1 opioid-exposed neonate born every 15 minutes.[1] This includes a 5-fold increase in the incidence of neonatal abstinence syndrome (NAS) between 2004 and 2014.[1] This increase has been sustained since that time.[2,3] Upward of 50%-80% of neonates exposed to opioids in utero develop NAS,[4-6] a pattern of withdrawal in neonates due to the abrupt discontinuation of prenatal opioids following delivery. Symptoms of NAS are highly variable[7,8] and can include autonomic instability, high-pitched cry, irritability, tremors, gastrointestinal disturbances, and feeding and sleeping difficulties.[9] Standard hospital policy is to place all opioid-exposed neonates on a 96-hour "hold" for observation,[10] as clinically significant signs that warrant pharmacologic treatment and prolonged hospitalization[11,12] may become apparent within 24 hours of birth until approximately 72 hours after birth. The average length of stay for pharmacologically treated neonates is 23 days.[13] This accounts for most of the estimated $2.5 billion annual cost of NAS,[2] most of which is covered by Medicaid[14] and results in prolonged separation of the mother and neonate, which can jeopardize their developing relationship.

Pharmacologic treatment for NAS is typically initiated when scores on observer rating scales, most often the Finnegan scale,[9] reach a "diagnostic" threshold. Although there is general consensus that the severity of NAS is quite variable,[12] there is no consensus on how to measure NAS severity. Single measures of NAS severity

Bayley-III	Bayley Scales of Infant and Toddler Development, Third Edition
BIC	Bayes information criterion
BSI	Brief Symptom Inventory
CBCL	Child Behavior Checklist
EI	Early intervention
LOS	Length of stay
LOT	Length of treatment
LPA	Latent profile analysis
NAS	Neonatal abstinence syndrome
NNNS	NICU Network Neurobehavioral Scale
RCT	Randomized controlled trial

From the [1]Brown Center for the Study of Children at Risk and Women and Infants Hospital, Providence, RI; [2]Department of Pediatrics, The Floating Hospital for Children at Tufts Medical Center, Boston, MA; [3]Tufts Clinical and Translational Science Institute, Boston, MA; [4]Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, MA; [5]Department of Pediatrics, Warren Alpert Medical School of Brown University and Women and Infants Hospital, Providence, RI; and [6]Department of Psychiatry and Human Behavior, Warren Alpert Medical School of Brown University, Providence, RI

Supported by the National Institute on Drug Abuse (R01 DA032889, to J.D. and B.L.). The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2020.08.034

are typically used, such as length of hospital stay (LOS), length of drug treatment (LOT), or the need for adjuvant therapy (eg, phenobarbital in addition to an opioid). However, these outcomes have not been systematically studied to determine how they relate to one another or how they might be combined into a useful clinical tool. A validated measure of NAS severity could have clinical implications for the treatment and management of neonates with prenatal opioid exposure and resulting NAS.

The present study is a secondary analysis of our previously reported randomized controlled trial comparing morphine and methadone for the treatment of infants with NAS.[15] In that study, the methadone-treated infants showed modest improvement in short-term outcomes. This study used presumptive measures of NAS severity to place neonates into statistically derived and mutually exclusive groups that could be used to identify or "index" high-risk neonates with the most significant NAS. We also included the NICU Network Neurobehavioral Scale (NNNS) for inclusion in the NAS severity index because it is a reliable tool for assessing opioid-exposed neonates and correlates with their long-term outcomes.[16] We then used these groups to predict developmental outcomes at age 18 months.

Methods

Patients

The study cohort comprised patients from a randomized clinical trial (RCT) (ClinicalTrials.gov: NCT01958476) conducted at 8 sites (Tufts Medical Center, Boston; Baystate Children's Hospital, Springfield, Massachusetts; Boston Medical Center, Boston; Maine Medical Center, Portland; UF Health, Jacksonville, Florida; University of Pittsburgh Medical Center, Pittsburgh; Vanderbilt University Medical Center, Nashville; and Women & Infants Hospital of Rhode Island, Providence).[15] Mothers treated with buprenorphine (33.6%) or methadone (62.9%) for an opioid use disorder or with an opioid treatment for chronic pain (3.5%) and receiving prenatal care were eligible for the study. A total of 117 infants required treatment, and 116 with parental consent were randomized to receive methadone or morphine between February 9, 2014, and March 6, 2017. Data were available on all 116 full-term neonates with NAS (58 males, 59 females) who required pharmacologic treatment (methadone, n = 58; morphine, n = 58) (**Figure 1**). The mean gestational age was 39.1 ± 1.1 weeks, and mean birth weight was 3157 ± 486 g.[15] Neonates in the study who

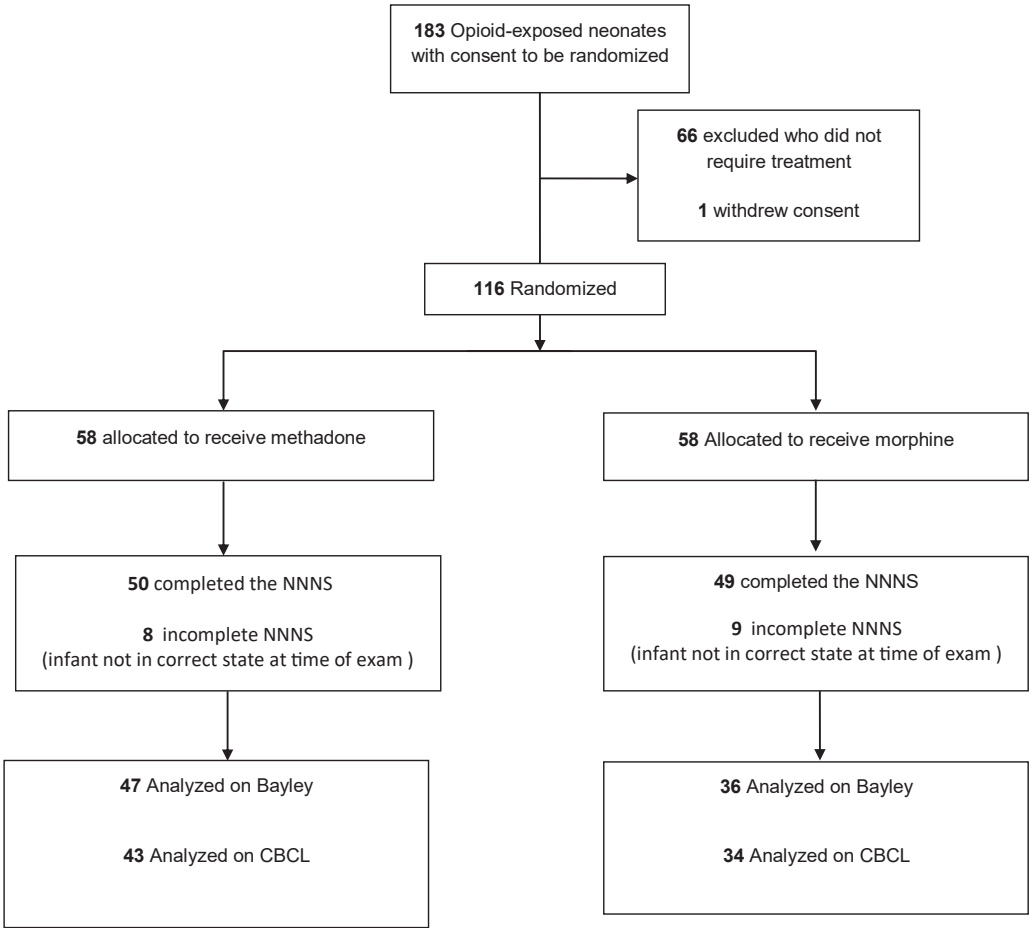

Figure 1. CONSORT flow diagram for ClinicalTrials.gov NCT01958476.

exceeded a predetermined opioid dose received phenobarbital. The study was approved by the Institutional Review Board at each site, and informed consent was obtained by study investigators.

Outcome Measures

Neurobehavioral assessment at hospital discharge was performed by certified examiners on 99 of 116 neonates (85%) using the NNNS. A comprehensive assessment of neonatal neurobehavior that examines neurologic integrity, behavioral function, and signs of stress,[17] the NNNS is used to assess high-risk neonates, including those with prenatal opioid exposure,[18-26] and correlates with long-term neurodevelopmental outcomes in this population.[16]

At approximately age 18 months, the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) was administered by certified examiners to 94 infants (81%). The Bayley-III includes cognitive, language, and motor composite scores, receptive and expressive communication, and fine and gross motor subscale scores compared with a normative control sample.[27] The Child Behavior Checklist (CBCL), a measure of behavioral problems identified in the infant,[28] was completed for 85 infants (73%) by the mother or primary caregiver. The CBCL consists of 100 statements about the child's behavior, with responses recorded as 0, not true; 1, somewhat or sometimes true; or 2, very true or often true. Items are grouped into syndromes (eg, aggressive behavior), and some syndromes are further demarcated into internalizing and externalizing problems. A total problem score from all questions is also derived. For each syndrome and problem scale and the total score, there are norms for normal (T score <60), borderline clinical (T score 60-63), and clinically significant (T score ≥64) scores.

As described previously, questionnaires were also administered to quantify caregiver and infant characteristics at the 18-month follow-up.[20] The Brief Symptom Inventory (BSI) assesses psychological distress with a self-reported questionnaire. The Global Severity Index of the BSI combines a number of symptoms and distress intensity and is an indicator of the respondent's distress level.[29] We also documented early intervention (EI) services, household composition, primary language spoken at home, infant medical problems, infant health and physical growth, infant medications, total number of emergency room visits since birth, postnatal maternal substance use, caregiver abuse, out-of-home placement, and Department of Child and Family Services involvement. These characteristics were all examined in relevant statistical analyses.

Statistical Analyses

The NNNS was analyzed using latent profile analysis (LPA), which grouped neonates into mutually exclusive categories using 12 NNNS summary scores. Membership for categorical latent profiles that represent heterogeneous subgroups was inferred from the 12 NNNS summary scores. LPA models with different numbers of profiles were fitted. We identified the model containing the optimal number of profiles via the Bayes information criterion (BIC) adjusted for sample size. The smallest BIC value indicates the best fit along with the bootstrapped likelihood ratio test and the number of cases in each profile. As the number of profiles increases, the sample-size adjusted BIC values decrease, indicating improved goodness of fit. The LPA analysis resulted in a 3-profile solution for the NNNS.

NAS severity clusters were developed using the two-step cluster method in SPSS (IBM, Armonk, New York).[30] First, this method generates subclusters based on variables selected a priori based on their prevalence in the published literature. The second step then uses these subclusters based on these variables to create homogenous subgroups that are maximally distinct from one another, as determined by the observed change in BIC between sequential cluster solutions. The variance among subclusters is maximized while minimizing the variance within subclusters. The second step uses the subclusters from the first step to once again group the data to determine the final clusters. In this case, 2 mutually exclusive groups were found, for which we examined Bayley-III and CBCL scores. Significance was considered at $P < .05$.

One-way ANOVA was used for continuous measures, and the χ^2 test was used for categorical measures to establish the covariates that should remain in our final 18-month outcome

Table I. Measures of NAS severity in infants in the high- and low-severity clusters

Measures of NAS severity	High-severity cluster (N = 21)	Low-severity cluster (N = 77)	*P* value
Length of stay, d, mean (SD)	31.48 (9.99)	17.97 (5.72)	<.001
Length of stay due to NAS, d, mean (SD)	27.33 (9.37)	14.87 (3.65)	<.001
Length of treatment, d, mean (SD)	25.33 (9.37)	12.87 (3.65)	<.001
Maximum Finnegan score, mean (SD)	13.71 (2.76)	12.48 (2.83)	.078
Total dose of study drug administered, mg, mean (SD)	35.05 (13.09)	10.83 (12.63)	<.001
Phenobarbital use, n (%)	19 (90.5%)	0 (0%)	<.001
Treatment drug (morphine) use, n (%)	15 (71.4%)	33 (42.9%)	.020
Atypical NNNS profile, n (%)	10 (47.6%)	14 (18.2%)	.005

Table II. Predictors in the high and low NAS severity clusters

Predictors	High-severity cluster (n = 21)	Low-severity cluster (n = 77)	*P* value
BSI score, mean (SD)	.69 (.76)	.48 (.56)	.235
Infant medical problems, mean (SD)	1.56 (1.72)	.98 (1.19)	.112
Maternal substance use, mean (SD)	1.94 (1.08)	2.05 (1.58)	.786
EI services, mean (SD)	.56 (.73)	.53 (.75)	.865
Maternal education less than high school, n (%)	2 (13.3)	11 (17.7)	.683
Child Protective Services involvement, n (%)	8 (44.4)	35 (57.4)	.333
Head circumference, cm, mean (SD)	33.0 (1.53)	34.1 (1.76)	.009
Male sex, n (%)	15 (71.4)	36 (46.8)	.045

Table III. Unadjusted and adjusted Bayley-III and CBCL scores of infants in the high and low NAS severity clusters

Parameters	High-severity cluster, unadjusted	Low-severity cluster, unadjusted	*P* value	High-severity cluster, adjusted	Low-severity cluster, adjusted	*P* value
Bayley-III*	n = 18	n = 65		n = 18	n = 65	
Cognitive composite	89.2 (3.5)	102.0 (2.5)	.013	91.4 (5.60)	98.7 (4.2)	.132
Language composite	83.6 (3.4)	98.4 (2.1)	.001	84.8 (5.2)	96.2 (3.9)	.013
Motor composite	94.2 (2.3)	103.6 (2.3)	.041	98.4 (4.9)	103.7 (3.6)	.211
CBCL†	n = 18	n = 59		n = 18	n = 59	
Internalizing	50.1 (3.4)	44.2 (1.3)	.051	50.3 (3.5)	47.7 (2.6)	.394
Externalizing	53.0 (2.5)	47.9 (1.4)	.083	52.8 (3.1)	50.0 (2.4)	.316
Total problems	53.7 (3.3)	46.9 (1.4)	.028	52.7 (3.4)	49.4 (2.5)	.274

Data are mean (SE).
*Adjusted for site, CPS involvement, sex, and head circumference.
†Adjusted for site, infant medical problems, sex, maternal postnatal substance use, maternal psychopathology, and head circumference.

analysis model. ANCOVA was used to adjust for covariates using Bonferroni correction. The covariates were based on published literature stating their associations with developmental outcomes.[20] Covariates included maternal psychopathology measured by the BSI, infant medical problems, maternal postpartum substance use, involvement of Child Protective Services, involvement in EI services, infant sex, maternal education (as a proxy for socioeconomic status), and study site (which was included a priori).[29,31-33] The data for the majority of covariates were collected via a maternal questionnaire and the BSI at the infant's 18-month follow-up appointment.

Results

Results of the cluster analysis showed 2 mutually exclusive groups, with 21 neonates in the high NAS severity group and 77 neonates in the low NAS severity group (**Table I**). One neonate was excluded from the cluster analysis because of missing data. Results of the LPA of the NNNS summary scores showed that the 3-profile solution provided the best model fit (**Figure 2**;[20] available at www.jpeds.com). Profile 3, an atypical profile, included 24 infants (24.2%). Compared with infants with the other profiles, infants with profile 3 required substantial handling, had poor regulation, had higher arousal and excitability, were hypertonic, had poor quality of movement, and had more signs of stress.

Compared with infants in the low NAS severity group, infants in the high NAS severity group had a longer LOS, a longer LOS due to NAS, a longer LOT due to NAS, and a higher total dose of the study drug (methadone or morphine) and were more likely to have received phenobarbital, to have been treated with morphine, and to have the atypical NNNS profile 3. The 2 groups did not differ in maximum Finnegan score. Analysis of the covariates showed that neonates in the high NAS severity group had a smaller head circumference and were more likely to be male (**Table II**).

At 18 months, Bayley-III data were available for 83 neonates and CBCL data were available for 77 neonates. The data on any measures of NAS severity did not differ between these patients and the 15 neonates without Bayley-III data and the 21 neonates without CBCL data. Unadjusted analyses showed that the low NAS severity group had higher scores on the Bayley Cognitive, Language, and Motor composite scores and fewer total behavior problems on the CBCL (**Table III**). In adjusted analyses, the only between-group difference that remained was on the Bayley Language composite.

Discussion

We examined NAS severity by combining commonly used individual severity measures. These measures were grouped statistically into 2 clusters that define high NAS and low NAS severity groups. With the exception of the maximum Finnegan score, all of the measures differed between the high and low NAS severity groups, suggesting that the measures are systematically related and supporting the construct validity of this NAS severity index. Support for the long-term predictive validity of this NAS severity index is suggested by our 18-month longitudinal findings. The unadjusted analysis showed differences between the high and low NAS severity groups on the Bayley-III and the CBCL. Critically, the differences in the Bayley Language composite were substantial (14.8 points unadjusted and 12.2 points adjusted) with the mean >1 SD below the Bayley standardized norm (ie, 100 ± 15). Male infants with a smaller head circumference in the high NAS severity group had the lowest Bayley Language composite scores. Thus, the combination of treatment with morphine, higher total dose of morphine or methadone, need for phenobarbital, longer LOS, longer LOS due to NAS, longer LOT due to NAS, atypical NNNS profile, male sex, and smaller head circumference put infants at greatest risk for later language delay.

With respect to the specific measures in our NAS severity index, variables related to LOS (ie, LOS, LOS due to treatment, and LOT due to NAS) have been the most widely used variables in the literature to estimate NAS severity.[10,12,34-41] Total dose of study drug (in our case treatment drug)[12,34,35,40-42] and use of adjunctive medications (eg, phenobarbital)[34,36,37,43] also have been used in previous studies, as has high (including maximum) Finnegan score,[12,34,40-42,44-46] although the latter did not contribute to our severity index. However, whether these various

measures are related to the severity of the underlying disorder, effects of the pharmacologic treatment (with potential for drug–drug interactions), or other biologic factors associated with NAS is not clear from these studies.

The inclusion of morphine as a contributor to NAS severity is unique and consistent with our previously reported RCT showing an association between morphine and significant increases in LOS, LOS due to NAS, and LOT compared with methadone.[15] The inclusion of the NNNS as an indicator of NAS severity is also unique. As mentioned earlier, the NNNS has been used in the study of NAS[10,18,19,22-24,40,47] but not as a measure of NAS severity. Our previous work with this RCT did not show differences in NNNS profiles between methadone-treated and morphine-treated neoantes.[20] Here we found that the atypical NNNS profile plays a role in NAS severity in the context of other NAS severity factors associated with worse long-term neurodevelopmental outcomes.

The concept of a NAS severity index is attractive for several reasons. First, it enables us to study variables in combination rather than alone, which could increase the validity and reliability of indicators of risk. Although the variables used in our cluster analysis were based on the literature, the clusters were derived statistically. Cluster analysis, in contrast to LPA, can treat cluster membership as an observed variable rather than a latent variable, is capable of handling a larger number of signs of NAS, and has been shown to perform well in choosing the number of clusters.[48] Our analysis comparing the variables between the high and low NAS severity groups supports the construct and concurrent validity of our NAS severity index, and the analysis using the NAS severity groups to predict 18-month outcome provides predictive validity for the index. In addition, we learned that the maximum Finnegan score might not belong in this group of NAS severity index variables, and that morphine and NNNS profiles do belong in this cluster of variables.

Another advantage of studying a combination of variables is that we are studying variables in the context of other variables (eg, in situ), which is likely to generate real-world data. For example, in our previously reported study comparing methadone and morphine for the treatment of NAS, we found no differences in Bayley-III or CBCL scores at 18 months between the 2 treatment groups, whereas in the present study we find that morphine is associated with language deficits in the high NAS severity group. In addition, current tools used to measure NAS, such as the Finnegan scale, have been characterized as highly variable and subjective,[6] and alternative assessment tools are needed to more accurately determine when an infant with NAS requires treatment. The inclusion of the atypical NNNS profile as part of the high NAS severity group is noteworthy, because although the dimension of neurobehavior has not been examined as a measure of NAS severity in previous work, a role of neurobehavior in the context of other medical factors would seem logical.

Neurobehavior also provides an additional opportunity for EI. The 18-month Bayley Language composite score (adjusted) was >20 points below the norm, beyond the <1 SD criteria for EI eligibility. The Bayley-III normative data are stratified on key demographic variables and use a sample collected in the United States, with 16% of the sample population having a score <85.[27] In fact, 10 of the 18 infants (55.6%) in the high NAS severity group scored <85 on the Bayley Language composite, more than 3 times the rate seen in the normative sample. Critically, we may have the ability to identify, among this population already at risk, which neonates are at greatest risk of NAS and ultimately abnormal neurodevelopmental outcome.

This same atypical NNNS profile has been related to long-term neurodevelopmental outcome, including IQ through age 4-1/2 years in infants with prenatal cocaine and opioid exposure.[16] It also identifies neurobehavioral domains that could provide specific targets from which to develop preventive interventions that could be of use to clinicians and EI providers. This information could be used at the time of initial hospital discharge to help determine how to allocate already limited resources and also used in a personalized medicine approach to develop targeted interventions to mitigate later developmental deficits in specific subgroups of high-risk neonates.

Another attractive potential use of the NAS severity index is to identify prenatal and perinatal measures that predict the onset and severity of NAS, possibly leading to preemptive interventions to mitigate NAS severity. For example, genetic,[49] epigenetic,[50] and nonpharmacologic treatment factors, such as rooming-in[4] and breast feeding,[39,44] have been shown to impact LOS and LOT. These and other factors could be used to predict which neonates are at greatest risk based on the NAS severity index, which could have short-term and long-term implications for the treatment and management of these neonates.

A limitation of this study is the questionable generalizability of our findings, for 2 reasons. First, although our selection of NAS severity variables was a priori (ie, based on the literature), our choice of variables was limited by what was available in our database. Second, the sample size was relatively small. Thus, our findings could be unique to this sample. In addition, our index cannot be used to identify high-risk neonates in clinical practice.

Nevertheless, these limitations aside, this report represents a first step in developing a NAS severity index. We encourage other investigators to explore these and other variables with different statistical techniques in larger samples and related populations of opioid-exposed infants to further expand the utility of an NAS severity index and evaluate its implications for clinical management. ■

Submitted for publication Apr 24, 2020; last revision received Jul 9, 2020; accepted Aug 12, 2020.

Reprint requests: Barry M. Lester, PhD, Women and Infants Hospital of Rhode Island, 101 Dudley Street, Providence, RI 02905. E-mail: Barry_Lester@Brown.edu

Data Statement

Data sharing statement available at www.jpeds.com.

References

1. Haight SC, Ko JY, Tong VT, Bohm MK, Callaghan WM. Opioid use disorder documented at delivery hospitalization—United States, 1999-2014. MMWR Morb Mortal Wkly Rep 2018;67:845-9.
2. Winkelman TNA, Villapiano N, Kozhimannil KB, Davis MM, Patrick SW. Incidence and costs of neonatal abstinence syndrome among infants with Medicaid: 2004-2014. Pediatrics 2018;141:e20173520.
3. Healthcare Cost and Utilization Project (H-CUP). Agency for Healthcare Research and Quality (AHRQ). Trends in neonatal abstinence syndrome births in the United States. 2018. https://www.hcup-us.ahrq.gov/reports/Trends_NeonatalAbstinenceSyndrome_Births_UnitedStates.pdf. Accessed March 20, 2020.
4. Holmes AV, Atwood EC, Whalen B, Beliveau J, Jarvis JD, Matulis JC, et al. Rooming-in to treat neonatal abstinence syndrome: improved family-centered care at lower cost. Pediatrics 2016;137:e20152929.
5. Ko JY, Patrick SW, Tong VT, Patel R, Lind JN, Barfield WD. Incidence of neonatal abstinence syndrome—28 states, 1999-2013. MMWR Morb Mortal Wkly Rep 2016;65:799-802.
6. Reddy UM, Davis JM, Ren Z, Greene MF. Opioid use in pregnancy, neonatal abstinence syndrome, and childhood outcomes: executive summary of a joint workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, American College of Obstetricians and Gynecologists, American Academy of Pediatrics, Society for Maternal-Fetal Medicine, Centers for Disease Control and Prevention, and the March of Dimes Foundation. Obstet Gynecol 2017;130:10-28.
7. American College of Obstetricians and Gynecologists (ACOG). Committee opinion No. 524: Opioid abuse, dependence, and addiction in pregnancy. Obstet Gynecol 2012;119:1070-6.
8. Kraft WK, Stover MW, Davis JM. Neonatal abstinence syndrome: pharmacologic strategies for the mother and infant. Semin Perinatol 2016;40:203-12.
9. Finnegan L, Kaltenbach K. Neonatal abstinence syndrome. In: Hoekelman RA, Friedman SB, Nelson NM, Seidel HM, eds. Primary pediatric care. 2nd ed. St. Louis: Mosby; 1992. p. 1367-78.
10. Jansson LM, Velez M. Neonatal abstinence syndrome. Curr Opin Pediatr 2012;24:252-8.
11. Hudak ML, Tan RC. Committee on Drugs; Committee on Fetus and Newborn; American Academy of Pediatrics. Neonatal drug withdrawal. Pediatrics 2012;129:e540-60.
12. Jones HE, Finnegan LP, Kaltenbach K. Methadone and buprenorphine for the management of opioid dependence in pregnancy. Drugs 2012;72:747-57.
13. Patrick SW, Davis MM, Lehmann CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009-2012. J Perinatol 2015;35:650-5.
14. Devlin L, Davis JM. A practical approach to neonatal opiate withdrawal syndrome. Am J Perinatol 2018;35:324-30.
15. Davis JM, Shenberger J, Terrin N, Breeze JL, Hudak M, Wachman EM, et al. Comparison of safety and efficacy of methadone vs morphine for treatment of neonatal abstinence syndrome: a randomized clinical trial. JAMA Pediatr 2018;172:741-8.
16. Liu J, Bann C, Lester B, Tronick E, Das A, Lagasse L, et al. Neonatal neurobehavior predicts medical and behavioral outcome. Pediatrics 2010;125:e90-8.
17. Lester BM, Tronick EZ, Brazelton TB. The Neonatal Intensive Care Unit Network Neurobehavioral Scale procedures. Pediatrics 2004;113(3 Pt 2):641-67.
18. Coyle MG, Ferguson A, Lagasse L, Oh W, Lester B. Diluted tincture of opium (DTO) and phenobarbital versus DTO alone for neonatal opiate withdrawal in term infants. J Pediatr 2002;140:561-4.
19. Jones HE, O'Grady KE, Johnson RE, Velez M, Jansson LM. Infant neurobehavior following prenatal exposure to methadone or buprenorphine: results from the Neonatal Intensive Care Unit Network Neurobehavioral Scale. Subst Use Misuse 2010;45:2244-57.
20. Czynski AJ, Davis JM, Dansereau LM, Engelhardt B, Marro P, Bogen DL, et al. Neurodevelopmental outcomes of neonates randomized to morphine or methadone for treatment of neonatal abstinence syndrome. J Pediatr 2020;219:146-51.e1.
21. Bada HS, Sithisarn T, Gibson J, Garlitz K, Caldwell R, Capilouto G, et al. Morphine versus clonidine for neonatal abstinence syndrome. Pediatrics 2015;135:e383-91.
22. Coyle MG, Ferguson A, LaGasse L, Liu J, Lester B. Neurobehavioral effects of treatment for opiate withdrawal. Arch Dis Child Fetal Neonatal Ed 2005;90:F73-4.
23. Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med 2010;363:2320-31.
24. Velez ML, Jansson LM, Schroeder J, Williams E. Prenatal methadone exposure and neonatal neurobehavioral functioning. Pediatr Res 2009;66:704-9.
25. Velez ML, McConnell K, Spencer N, Montoya L, Tuten M, Jansson LM. Prenatal buprenorphine exposure and neonatal neurobehavioral functioning. Early Hum Dev 2018;117:7-14.
26. Lester BM, Tronick EZ, LaGasse L, Seifer R, Bauer CR, Shankaran S, et al. The maternal lifestyle study: effects of substance exposure during pregnancy on neurodevelopmental outcome in 1-month-old infants. Pediatrics 2002;110:1182-92.
27. Bayley N. Bayley Scales of Infant and Toddler Development (Bayley-III): administration manual. 3rd ed. Pearson; 2006.
28. Achenbach TM, Rescorla L. Manual for the ASEBA preschool forms and profiles: an integrated system of multi-informant assessment. Burlington: University of Vermont; 2000.
29. Derogatis LR, Melisaratos N. The Brief Symptom Inventory (BSI): an introductory report. Psychol Med 1983;13:595-605.
30. IBM Corp. IBM SPSS statistics for Windows, version 24.0. Armonk, NY: IBM; 2016.
31. Wilson GS, Desmond MM, Verniaud WM. Early development of infants of heroin-addicted mothers. Am J Dis Child 1973;126:457-62.
32. Kerker BD, Zhang J, Nadeem E, Stein REK, Hurlburt MS, Heneghan A, et al. Adverse childhood experiences and mental health, chronic medical conditions, and development in young children. Acad Pediatr 2015;15:510-7.
33. van der Sluis S, Polderman TJC, Neale MC, Verhulst FC, Posthuma D, Dieleman GC. Sex differences and gender-invariance of mother-reported childhood problem behavior. Int J Methods Psychiatr Res 2017;26:e1498.
34. Abdel-Latif ME, Pinner J, Clews S, Cooke F, Lui K, Oei J. Effects of breast milk on the severity and outcome of neonatal abstinence syndrome among infants of drug-dependent mothers. Pediatrics 2006;117:e1163-9.
35. Abrahams RR, Kelly SA, Payne S, Thiessen PN, Mackintosh J, Janssen PA. Rooming-in compared with standard care for newborns of mothers using methadone or heroin. Can Fam Physician 2007;53:1722-30.
36. Allocco E, Melker M, Rojas-Miguez F, Bradley C, Hahn KA, Wachman EM. Comparison of neonatal abstinence syndrome manifestations in preterm versus term opioid-exposed infants. Adv Neonatal Care 2016;16:329-36.
37. Bakhireva LN, Holbrook BD, Shrestha S, Leyva Y, Ashley M, Cano S, et al. Association between prenatal opioid exposure, neonatal opioid withdrawal syndrome, and neurodevelopmental and behavioral outcomes at 5-8 months of age. Early Hum Dev 2019;128:69-76.
38. Charles MK, Cooper WO, Jansson LM, Dudley J, Slaughter JC, Patrick SW. Male sex associated with increased risk of neonatal abstinence syndrome. Hosp Pediatr 2017;7:328-34.
39. Cirillo C, Francis K. Does breast milk affect neonatal abstinence syndrome severity, the need for pharmacologic therapy, and length of stay for infants of mothers on opioid maintenance therapy during pregnancy? Adv Neonatal Care 2016;16:369-78.
40. Coyle MG, Salisbury AL, Lester BM, Jones HE, Lin H, Graf-Rohrmeister K, et al. Neonatal neurobehavior effects following buprenorphine versus methadone exposure. Addiction 2012;107:63-73.
41. Jansson LM, DiPietro JA, Elko A, Velez M. Infant autonomic functioning and neonatal abstinence syndrome. Drug Alcohol Depend 2010;109:198-204.
42. Kaltenbach K, Holbrook AM, Coyle MG, Heil SH, Salisbury A, Stine S, et al. Predicting treatment for neonatal abstinence syndrome in infants born to women maintained on opioid agonist medication. Addiction 2012;107:45-52.
43. Isemann B, Meinzen-Derr J, Akinbi H. Maternal and neonatal factors impacting response to methadone therapy in infants treated for neonatal abstinence syndrome. J Perinatol 2011;31:25-9.

44. Hytinantti T, Kahila H, Renlund M, Järvenpää AL, Halmesmäki E, Kivitie-Kallio S. Neonatal outcome of 58 infants exposed to maternal buprenorphine in utero. Acta Paediatr 2008;97:1040-4.
45. McQueen KA, Murphy-Oikonen J, Gerlach K, Montelpare W. The impact of infant feeding method on neonatal abstinence scores of methadone-exposed infants. Adv Neonatal Care 2011;11:282-90.
46. Nellhaus EM, Nieuwenhuizen L, Egleton R, Hansen Z, Chaffin D, Loudin S, et al. History of postpartum depression as a contributor to the severity of NAS. Addict Behav 2019;89:78-84.
47. Heller NA, Logan BA, Morrison DG, Paul JA, Brown MS, Hayes MJ. Neonatal abstinence syndrome: neurobehavior at 6 weeks of age in infants with or without pharmacological treatment for withdrawal. Dev Psychobiol 2017;59:574-82.
48. Tibshirani R, Walther G, Hastie T. Estimating the number of clusters in a data set via the gap statistic. J R Stat Soc Ser B Stat Methodol 2001;63:411-23.
49. Wachman EM, Hayes MJ, Brown MS, Paul J, Harvey-Wilkes K, Terrin N, et al. Association of OPRM1 and COMT single-nucleotide polymorphisms with hospital length of stay and treatment of neonatal abstinence syndrome. JAMA 2013;309:1821-7.
50. Wachman EM, Hayes MJ, Lester BM, Terrin N, Brown MS, Nielsen DA, et al. Epigenetic variation in the mu-opioid receptor gene in infants with neonatal abstinence syndrome. J Pediatr 2014;165:472-8.

50 Years Ago in *The Journal of Pediatrics*

Down syndrome: Creases to chromosomes

Reed TE, Borgaonkar DS, Conneally PM, Yu P, Nance WE, Christian JC, et al. Dermatoglyphic nomogram for the diagnosis of Down's syndrome. J Pediatr 1970;77:1024-32.

"Dermatoglyphics" was a term coined in 1926 to describe the study of the ridges and lines in the skin for research in human anthropology and other scientific fields. Cummins, in collaboration with Ralph Victor Platou, head of Tulane's Department of Pediatrics, described the dermatoglyphic abnormalities in children with Down syndrome (trisomy 21) in 1950. In 1957, when chromosomal analysis was not possible, Norma Ford Walker described a diagnostic scoring system for Down syndrome that relied heavily on dermatoglyphics.[1]

Fifty years ago, Reed et al published a report on dermatoglyphic nomograms for the diagnosis of Down syndrome and identified 4 major variables that could identify 81% of individuals with Down syndrome: the right hallux pattern, the right ATD angle, and the patterns of both index fingers.

The 1960s and 1970s were the era of dermatoglyphics, when numerous scientific papers on Down syndrome and other genetic disorders were published. In few studies, parents of children with Down syndrome showed some dermatoglyphic abnormalities, but not specific enough to identify individuals with increased risk to offspring.[2] Dermatoglyphic patterns observed in patients with Alzheimer's disease closely correspond with patterns observed in Down syndrome, suggesting that a common genetic factor may be involved in epidermal ridge formation in fetal development, meiotic nondisjunction during gametogenesis, and accelerated neuronal senescence.[3]

Gradually, interest in and the importance of this discipline declined due to various reasons. The digital patterns observed in conditions of Down syndrome were nonspecific, being observed on the hands and fingers of normal individuals as well, and a specific pattern was not seen in all patients with Down syndrome. Moreover, evaluation of all digital patterns is cumbersome and difficult in a clinical setting. With the advancements in the field of molecular genetics, this fascinating field has lost its significance in the current era.[4] Simian crease is now the sole remnant of this field that is still referred to in evaluation of Down syndrome.

Sankar Vaikom Hariharan, MD, DM
SAT Hospital
Government Medical College
Thiruvananthapuram, Kerala, India

Piyush Gupta, MD, FAMS
University College of Medical Sciences
Delhi, India

References

1. Walker NF. The use of dermal configurations in the diagnosis of mongolism. J Pediatr 1957;50:19-26.
2. Schmidt R, Dar H, Nitowsky HM. Dermatoglyphic and cytogenetic studies in parents of children with trisomy 21. Clin Genet 1981;20:203-10.
3. Weinreb HJ. Dermatoglyphic patterns in Alzheimer's disease. J Neurogenet 1986;3:233-46.
4. Asen D. Secrets in fingerprints: clinical ambitions and uncertainty in dermatoglyphics. CMAJ 2018;190:E597-9.

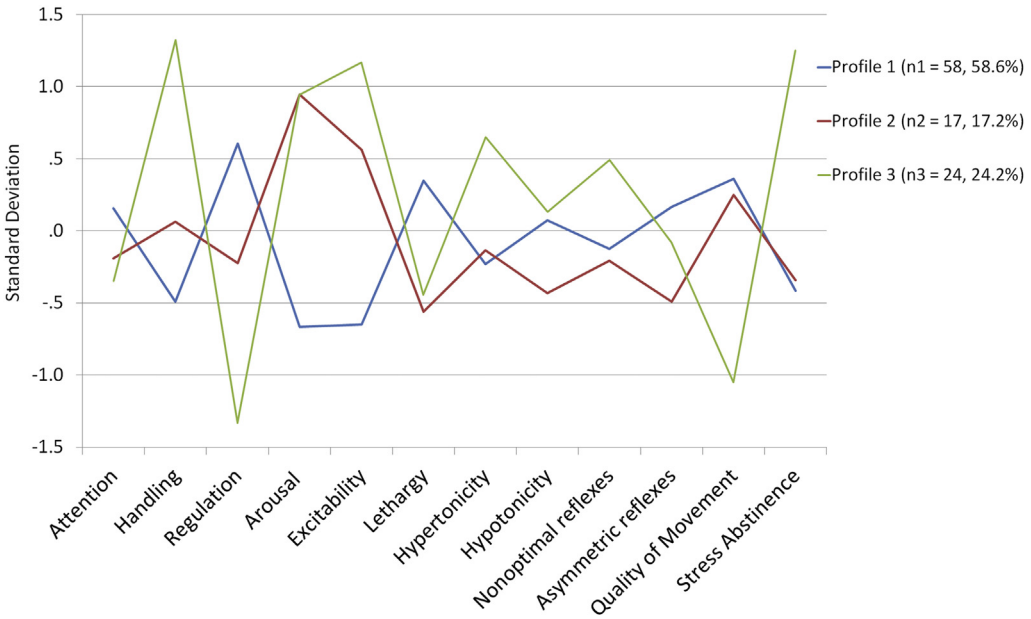

Figure 2. NNNS profiles at hospital discharge. (Reprinted from Czynski AJ, Davis JM, Dansereau LM, Engelhardt B, Marro P, Bogen DL, et al. Neurodevelopmental outcomes of neonates randomized to morphine or methadone for treatment of neonatal abstinence syndrome. J Pediatr 2020;219:146-51.e1.[20]).