Neurotoxicology and Teratology 34 (2012) 47–55

Contents lists available at SciVerse ScienceDirect

Neurotoxicology and Teratology

journal homepage: www.elsevier.com/locate/neutera

A pilot study of preemptive morphine analgesia in preterm neonates: Effects on head circumference, social behavior, and response latencies in early childhood

Sherry A. Ferguson [a,b,*], Wendy L. Ward [b], Merle G. Paule [a,b], R. Whit Hall [b,c], K.J.S. Anand [b,d]

[a] Division of Neurotoxicology, National Center for Toxicological Research/Food and Drug Administration, Jefferson, AR, United States
[b] Department of Pediatrics, Arkansas Children's Hospital, Little Rock, AR, United States
[c] Division of Neonatology, University of Arkansas for Medical Sciences, Little Rock, AR, United States
[d] Department of Pediatrics, Division of Critical Care Medicine, Le Bonheur Children's Hospital, University of Tennessee Health Science Center, Memphis, TN, United States

ARTICLE INFO

Article history:
Received 3 June 2011
Received in revised form 28 October 2011
Accepted 31 October 2011
Available online 07 November 2011

Keywords:
Prematurity
Morphine
Preemptive analgesia
Neuropsychology
Cognition
Delayed matching to sample

ABSTRACT

Use of preemptive analgesia in Neonatal Intensive Care Units is recommended for severe and/or invasive procedures. However, the potential long-term consequences of such analgesia, which may be prolonged, are only beginning to be studied. In this pilot study, a subset of subjects previously enrolled in the Neurological Outcomes and Preemptive Analgesia in Neonates (NEOPAIN) trial was assessed at early childhood. These ex-preterm infants (born at 23–32 weeks of gestational age) required intubation within 72 h postpartum and were randomized to receive either preemptive morphine analgesia (maximum of 14 days) or placebo within 8 h post-intubation. At 5–7 years of age, neuropsychological outcomes, morphometrics, adaptive behavior, parent-rated behavior, motivation, and short-term memory were measured. Although overall IQ and academic achievement did not differ between the morphine treated (n = 14) and placebo (n = 5) groups, preemptive morphine analgesia was associated with distinct differences in other outcome variables. Head circumference of morphine treated children was approximately 7% smaller (Cohen's d: 2.83, effect size large) and body weight was approximately 4% less (Cohen's d: 0.81, effect size large); however, height did not differ. In the short-term memory task (delayed matching to sample), morphine treated children exhibited significantly longer choice response latencies than placebo children (3.86 ± 0.33 and 2.71 ± 0.24 s, respectively) ($p < 0.03$) and completed approximately 27% less of the task than placebo children (Cohen's d: 0.96, effect size large). Parents described morphine treated children as having more social problems, an effect specific to creating and maintaining friendships (Cohen's d: −0.83, effect size large). Despite the small sample size and the preliminary nature of this study, these results are strongly suggestive of long-lasting effects of preemptive morphine analgesia. A larger investigation with more comprehensive assessments of some of these key features will enable a more complete understanding of the relationship between preemptive morphine treatment and long-term neurocognitive, behavioral, and adaptive outcomes.

Published by Elsevier Inc.

1. Introduction

Preterm neonates in Neonatal Intensive Care Units (NICUs) repetitively experience painful procedures (intubations, heel lances, tracheal suctioning, etc.). In the U.S. and elsewhere, the number of such procedures has been estimated at 5–15 per infant/day (Anand et al., 1996; Barker and Rutter, 1995; Carbajal et al., 2008; Johnston et al., 1997; Porter and Anand, 1998; Simons et al., 2003). Although there is some controversy regarding the use of pharmacological agents for minor or less invasive procedures (Kumar, 2008), there is agreement that preemptive analgesia is recommended for more severe or invasive procedures, (American Academy of Pediatrics et al., 2000; American Academy of Pediatrics (Committee on Fetus and Newborn et al., 2000; Anand et al., 2006; D'Apolito, 2006; Hall et al., 2007).

Pharmacological interventions for pain management in preterm neonates are supported by clinical and experimental evidence (reviewed in Anand et al., 2006); however, much remains to be understood before routine use is incorporated into daily practice. For example, the pharmacokinetics/pharmacodynamics of repeated analgesic treatment in the neonate are only beginning to be described (Anand et al., 2008). Less known, however, are the long-term global effects of neonatal analgesia (see American Academy of Pediatrics (Committee on Fetus and Newborn et al., 2000; Anand et al., 2006; Bellu et al., 2010; Fitzgerald and Walker, 2009; Hall et al., 2007) for the need for followup studies). Given the long-term neurological impact of untreated neonatal pain (Fitzgerald and Walker, 2009), it is essential to determine the long-term effects of preemptive analgesia.

Several randomized trials have begun to evaluate the efficacy of preemptive analgesia in neonates; specifically, opiate and sedative

* Corresponding author at: HFT-132, Division of Neurotoxicology, National Center for Toxicological Research/FDA, 3900 NCTR Road, Jefferson, AR 72079, United States. Tel.: +1 870 543 7589; fax: +1 870 543 7745.
E-mail address: Sherry.Ferguson@fda.hhs.gov (S.A. Ferguson).

0892-0362/$ – see front matter. Published by Elsevier Inc.
doi:10.1016/j.ntt.2011.10.008

treatment (e.g., Anand et al., 2004; Quinn et al., 1992, 1993; Roze et al., 2008). Three have described long-term outcomes of such analgesia (de Graaf et al., 2011; MacGregor et al., 1998; Roze et al., 2008). Specifically, short-term (≤ 5 or 7 days) morphine treatment of preterm neonates did not alter IQ, motor development, or behavioral problems measured at 5–6 years of age (de Graaf et al., 2011; MacGregor et al., 1998). However, the visual analysis subtest of an IQ assessment indicated poorer performance in morphine treated 5-year-old children (de Graaf et al., 2011). Longer term (> 7 days) unspecified sedative and/or opiate exposure had no effects on cognitive ability measured at 5 years of age after adjusting for illness severity (Roze et al., 2008).

Here, we report preliminary long-term outcomes from the Neurological Outcomes and Preemptive Analgesia in Neonates (NEOPAIN) trial, a randomized placebo-controlled trial which hypothesized that preemptive morphine analgesia would improve neurological outcomes in ventilated preterm neonates. Subjects in the NEOPAIN have not been assessed since NICU discharge and are now school-age. Although many preterm neonates develop cognitive deficits or learning disabilities (reviewed in Allen, 2008), it is possible that prior morphine exposure may have altered such outcomes. This initial assessment was conducted following those suggestions for studies of long-term outcomes such as use of well-defined measures (American Academy of Pediatrics (Committee on Fetus and Newborn et al., 2000; Anand et al., 2006) and measurement of executive function and memory (Anand et al., 2006). A small subset of subjects from the NEOPAIN trial in central Arkansas were administered a brief physical exam followed by assessments of cognitive, personal and social skills, and behavioral problems. Operant behavior assessed aspects of motivation and short-term memory since performance on these tasks has been previously described for preterm children (Paule et al., 1999) and could be easily compared with those of subjects in this study.

2. Methods

2.1. NEOPAIN trial study design

The NEOPAIN study design including inclusion/exclusion criteria, maternal and neonatal characteristics, stratification of neonates, morphine doses and duration are described in detail in the original paper (Anand et al., 2004). Briefly, very premature infants born between 23 and 32 weeks of gestational age and requiring intubation within the first 72 h were randomized to receive either preemptive morphine analgesia or placebo within 8 h post-intubation. Morphine dose regimens were based on gestational age. Due to ethical considerations, additional analgesia with open-label morphine was permitted in either group with additional guidelines for the use of phenobarbital, opiate antagonists, and muscle relaxants. Use of midazolam and other sedatives was not permitted. Criteria for the weaning and withdrawal of morphine were defined *a priori*. Preemptive analgesic use was permitted for a maximum of 14 days. There were no differences in the clinical and demographic characteristics of the two randomized groups.

2.2. Participant recruitment and inclusion/exclusion criteria

Phone contact was attempted with the 196 parents/guardians of the 212 formerly preterm neonates (some subjects were twins; total n = 96 morphine treated, n = 116 placebo) who were enrolled in the central Arkansas area NEOPAIN cohort. Of those 196, there was no working phone number (or the number was continually busy or was not answered) for 117 (n = 51 morphine treated, n = 66 placebo). Of those contacted, 28 (n = 11 morphine treated, n = 17 placebo) did not respond to phone messages, scheduled a testing appointment but later cancelled, were interested but did not schedule an appointment, were ineligible, or were not interested. Final participation consisted of 14 morphine treated (8 male and 6 female) and 5 placebo (4 male and 1 female) children. Participation did not affect or alter the child's medical treatment.

Five general criteria were used for inclusion in the current study: 1) the child must have been enrolled in the original NEOPAIN trial during their NICU course at Arkansas Children's Hospital or the University of Arkansas for Medical Sciences, 2) the child must be 5–7 years of age, 3) if 7 years of age, the child must provide assent, and 4) because stimulant medication has been shown to have effects on the operant tasks assessed here (Chelonis et al., 2011 Chelonis et al., 2002), the child must be able to remain stimulant-medication free for 18 h prior to testing. Exclusion criteria were: 1) the parent/guardian was not available or willing to give consent, 2) the family lived more than 75 miles from Little Rock, AR (the testing site), 3) the child had documented severe neurocognitive deficits (e.g., cerebral palsy), chronic ventilator dependency, neurosensory deficits (e.g., deafness), or other chronic problems (e.g., chronic renal or hepatic failure), 4) the parent/guardian or child had a significant language barrier (some test materials were available only in English), or 5) the child was unable to or their parent/guardian did not allow them to remain stimulant-medication free for 18 h prior to testing.

The original NEOPAIN protocol was approved by the University of Arkansas for Medical Sciences (UAMS) Institutional Review Board. Procedures and testing materials for this follow-up study were approved by: 1) the UAMS Institutional Review Board and, 2) the Food and Drug Administration's Research Involving Human Subjects Committee. Written informed consent from the parent/guardian and written informed assent from the single 7-year-old subject were obtained before enrollment. The parent/guardian was present when the assent form was read to the subject. Parents were offered a copy of the consent form and could withdraw consent at anytime during the study.

2.3. Procedures

2.3.1. Parent-completed questionnaires

The parent/guardian completed a brief demographic questionnaire, the Child Behavior Checklist – Parent version (ages 6–18) (ASEBA, Burlington, VT), the Conners' Comprehensive Behavior Rating Scales – Parent Form (Pearson Assessments, San Antonio, TX), and the Vineland Adaptive Behavior Scales (Second Edition) (Pearson Assessments, San Antonio, TX). The Child Behavior Checklist yields three composite scores: Internalizing and Externalizing Syndromes and a Total Problems score. The Vineland Adaptive Behavior Scales consists of 13 subdomain scores which are compiled into five domains (Communication, Daily Living, Socialization, Motor Skills, and Maladaptive Behavior) as well as a total Adaptive Behavior Composite score. The Conners' Comprehensive Behavior Rating Scales contains 8 content scales, 3 global indices, and 3 symptom scales to assess attention deficits and hyperactivity disorders.

2.3.2. Physical exam

A pediatrician (KJSA or RWH) blind to experimental group conducted a brief physical exam of the child. Height, weight, head circumference and body mass index (BMI) (kg/m^2) were obtained. The physical exam included assessments of neurologic soft signs and a brief medical history to determine the presence of hearing, vision, or attentional problems.

2.3.3. Neuropsychological assessments

Trained psychological examiners blind to experimental group administered the Stanford–Binet test (Version 5) (Riverside Publishing, Rolling Meadows, IL) followed by the Wide Range Achievement Test (WRAT4) (Psychological Assessment Resources, Inc., Lutz, FL). The Stanford–Binet provides a full-scale IQ, two domain scores (Nonverbal IQ and Verbal IQ), and five factor indices: fluid reasoning, knowledge, quantitative processing, visual-spatial processing, and working

memory. Sentence comprehension, word reading, spelling, math computation, and reading composite were WRAT4 metrics.

2.3.4. Operant tests

After the neuropsychological assessments, each child performed a Progressive Ratio (PR) task followed by a Delayed Matching to Sample (DMTS) task. The apparatus and tasks have been described in detail (Paule et al., 1988). Briefly, the response panel contained two types of response manipulanda (press-plates and response levers). Below the response panel was a tray into which reinforcers (nickels) were delivered. Video-recorded instructions were shown to the child before each task. A maximum of $4.50 in reinforcers could be earned by the child which he or she was allowed to keep.

The PR task began when the far right of four response levers (aligned horizontally) was extended from the response panel. Lever presses were reinforced with a nickel based on a PR 1 + 10 schedule. Specifically, after the first lever press, a reinforcer was delivered. The number of lever presses required to obtain each subsequent reinforcer was then increased by 10. Thus, the first reinforcer "cost" 1 lever press, the second cost 11 lever presses, the third 21, and so on. The task continued until 30 nickels were earned or 10 min had elapsed. The total number of reinforcers earned was used for statistical analyses.

Three press-plates aligned horizontally above the retractable levers on the response panel were used for the DMTS task: one of seven white-on-black geometric symbols (e.g., circle, square, triangle) could be projected onto each press-plate. The task began with one of the seven stimuli (the sample stimulus) presented on the center press-plate. This sample stimulus remained illuminated until the subject pressed it after which it was darkened and a delay (1, 2, 4, 8, 16, or 32 s) was initiated. Following the delay, each press-plate was illuminated with a different symbol, one of which was the same as had initially appeared on the center press-plate (sample). If the subject pressed the stimulus matching the sample, a reinforcer was dispensed and the next trial began immediately with presentation of a sample stimulus. However, if the subject pressed one of the two stimuli that did not match the sample, all press-plates were darkened and a 10 s timeout began, after which the next trial began. The DMTS task continued until 60 nickels were earned or 20 min had elapsed. Endpoints analyzed were: 1) percent task completed (100*(total number of reinforcers earned/60), 2) accuracy (100*(total number of correct trials/total number of trials presented), 3) average observing response latency (average time between presentation of the sample stimulus and the press-plate response), 4) average choice response latency (average time between presentation of the three stimuli and the press-plate response), 5) average correct choice response latency (for those trials that resulted in a correct response), and 6) average incorrect choice response latency (for those trials that resulted in an incorrect response).

2.4. Statistical analyses

For most endpoints, an analysis of variance (ANOVA) with experimental group and sex as factors determined statistical significance. Although there was only one female in the placebo group, the variance is assumed constant across sexes and treatment groups. Thus, the data for this subject is assumed to be representative of the mean for placebo females. For the DMTS task, an additional factor of delay interval was included for the analyses of accuracy, average observing response latency, and average choice response latency (correct and incorrect). Height, weight, head circumference, and BMI were analyzed with analyses of covariance using age as a covariate.

Traditional statistical significance is influenced by sample size and at best, we obtained group sizes of 14 and 5 for the morphine-treated and placebo groups, respectively. Significance testing with small sample sizes is especially prone to Type II errors. As noted by Zakzanis, a meaningful effect may be present but the statistical test may lack sufficient power for detection (Zakzanis, 2001). Thus, as advised by the American Psychological Association (American Psychological et al., 2009) and as advocated for behavioral pediatrics specifically (Colliver, 2007), effect sizes were calculated for each endpoint. Effect sizes describe the magnitude of the effect, are independent of sample size, scale-free, and they aid in the interpretation of the substantive or practical significance of a result. Since it has been suggested to be the most appropriate for neuropsychological research (Zakzanis, 2001), Cohen's d measure was calculated using the modified formula which takes into account smaller sample bias (Durlak, 2009). Only those endpoints which resulted in statistical significance and/or a large effect size ($\geq$0.80 as defined by Cohen Cohen, 1994) were considered to definitively distinguish the two experimental groups. Discussion of a large effect size which was not statistically significant is not only appropriate, but has been encouraged (Thompson, 1999).

3. Results

Table 1 shows the demographic characteristics of the subjects. Of the five placebo subjects, four received additional analgesia (3 males and 1 female). Of the 14 morphine treated subjects, 13 received additional analgesia (7 males and 6 females). Included in Table 1 are the percentages of the original Arkansas NEOPAIN cohort, excluding those that died prior to 28 days of age. These percentages are included for comparison to the demographics of the current subjects.

3.1. Physical exam

Table 2 shows data and effect sizes for each group by sex. There were no statistically significant effects of group, sex, or their interaction in the analyses of height, body weight, head circumference, or BMI. However, body weight and head circumference indicated large effect sizes (0.81 and 2.83, respectively), indicating decreased body weight and head circumference in the morphine treated group (see Fig. 1A and B for individual data). Neurological soft sign abnormalities were noted in 2/14 children in the morphine treated group and 1/5 in the placebo treated group. These differences were not significant.

3.2. Parent-completed questionnaires and neuropsychological assessments

Table 3 shows data and effect sizes for each endpoint by group and sex.

3.2.1. Stanford–Binet, Child Behavior Checklist – Parent Version, and WRAT4

None of the 8, 11, or 5 endpoints from the Stanford–Binet, the Child Behavior Checklist, or the WRAT4, respectively, indicated statistically significant effects of group, sex, or their interaction.

3.2.2. Vineland Adaptive Behavior Scales

None of the 5 domain scores or the adaptive Behavior Composite score indicated statistically significant effects of group, sex, or the interaction. However, the Socialization domain as well as the total Adaptive Behavior Composite score indicated large effect sizes (see Table 3). These two effect sizes resulted from comparing one male placebo subject to 11 morphine subjects, given that similar scores could not be computed for the other 8 subjects (due to the scoring criteria). It is not clear how representative this single placebo subject was of the entire group; thus, these two large effects will not be discussed further.

3.2.3. Conners' Comprehensive Behavior Rating Scales

None of the endpoints from the Conners' Comprehensive Behavior Rating Scales indicated statistically significant effects of group, sex, or the interaction. However, the social problems score indicated a large

Table 1
Subject characteristics.

		Placebo		Morphine	
		Boys (n = 4)	Girls (n = 1)	Boys (n = 8)	Girls (n = 6)
	Months of age at testing	74.3 ± 4.2	75.9	71.2 ± 2.2	77.0 ± 3.4
Child's race	White[a]	4 *(61.0%)*[b]	1 *(46.8%)*	7 *(72.7%)*	6 *(60.8%)*
	Black	0 *(37.3%)*	0 *(51.6%)*	1 *(21.8%)*	0 *(37.3%)*
Gestational age (weeks) at birth	23–26	1 *(35.6%)*	0 *(24.2%)*	4 *(27.3%)*	2 *(21.6%)*
	27-29	3 *(42.4%)*	1 *(56.5%)*	3 *(54.6%)*	2 *(51.0%)*
	30-32	0 *(22.0%)*	0 *(19.4%)*	1 *(18.2%)*	2 *(27.5%)*
Mother's marital status	Single	0 *(56.0%)*	0 *(71.0%)*	1 *(49.1%)*	1 *(58.8%)*
	Divorced	1 *(0%)*	0 *(0%)*	1 *(1.9%)*	0 *(0%)*
	Married	3 *(44.1%)*	1 *(29.0%)*	5 *(47.3%)*	4 *(41.2%)*
Mother's education	Grades 10–12	3	1	5	1
	Associate's degree	0	0	0	0
	Bachelor's degree	1	0	1	2
	Master's degree	0	0	1	2
	Doctorate or Professional degree	0	0	0	
Father's education	Grades 10–12	2	1	3	3
	Associate's degree	0	0	2	0
	Bachelor's degree	0	0	0	1
	Master's degree	1	0	1	0
	Doctorate or Professional degree	0	0	0	

[a] Numbers in each category may not sum to total as the parent/guardian may not have answered all questions.
[b] Italicized percentages in parentheses represent the percent of the original Arkansas NEOPAIN cohort for each sex/treatment group after elimination of neonatal mortality (i.e., death before 28 days of age). These are shown for representative comparisons to the current study numbers. Percentages may not sum to 100 due to rounding. There was an additional race category (Hispanic) in the original cohort. Finally, percentage comparisons for mother's education could not be calculated as the original educational categories were different and percentage comparisons for father's education could not be calculated as this information was not collected in the original cohort study.

effect size (−0.83) and signified increased social problems in the morphine treated group. This effect size resulted from scores from all subjects (i.e., 5 placebo and 14 morphine treated children).

3.3. Operant tests

Two subjects were not assessed for PR and DMTS performance: one morphine treated male had taken Ritalin the morning of the test session and one morphine treated female did not participate. Two additional subjects were not included in the final DMTS analyses: one morphine treated female did not complete at least one trial at each delay (a requirement for statistical inclusion) and one morphine treated male requested to terminate the test session after the PR task ended. This resulted in final subject numbers for the DMTS task of 4 placebo males, 1 placebo female, 6 morphine treated males and 4 morphine treated females. Table 4 shows effect size and data for each operant test endpoint by group and sex.

3.3.1. Progressive ratio

Analysis of number of reinforcers earned did not yield significant effects of group, sex, or the interaction. Average number of reinforcers earned ranged 12–15 for each group, which translated into 121–154 lever presses emitted for the last reinforcer earned.

3.3.2. Delayed matching to sample

Analyses of percent task completed, accuracy, and average observing response latency did not indicate significant effects of group, sex, or the interaction. However, percent task completed indicated a large effect size (0.96) and revealed that less of the task was completed by the morphine treated group. Choice response latency indicated a significant effect of group ($F(1,11) = 6.36$, $p < 0.03$). The morphine treated group had longer choice response latencies (3.86 ± 0.33 and 2.71 ± 0.24 s, respectively, averaged over sex). There was a significant effect of group ($F(1,11) = 6.08$, $p < 0.04$) for average correct choice response latency. The morphine group exhibited longer choice response latencies for correct trials than did the placebo group (3.75 ± 0.44 vs. 2.48 ± 0.51 s, respectively, averaged over sex). However, average incorrect choice response latencies did not differ between groups ($F(1,10) = 0.86$, $p < 0.38$) (5.33 ± 0.42 and 5.64 ± 1.34 s for the morphine and placebo treated groups, respectively, averaged over sex).

4. Discussion

In this pilot study, preemptive analgesia with morphine in preterm infants had no significant effects on IQ, academic achievement, self-sufficiency, or motivational assessments at 5–7 years of age. Head circumference and body weight, however, were decreased in the morphine treated group. Further, via parent report on the Conners' Comprehensive

Table 2
Effect size and mean (± SEM) of physical exam parameters[a].

		Placebo		Morphine	
	Cohen's d[b]	Boys (n = 4)	Girls (n = 1)	Boys (n = 8)	Girls (n = 6)
Height (cm)	0.52	116.88 ± 1.66	114.20	115.05 ± 1.74	115.12 ± 1.28
Weight (kg)	**0.81**	22.27 ± 1.47	19.80	19.58 ± 0.78	20.59 ± 1.62
BMI	0.10	16.32 ± 1.07	15.18	14.86 ± 0.73	15.56 ± 1.25
Head circumference (cm)	**2.83**	52.35 ± 0.96	50.80	48.63 ± 1.79	47.27 ± 1.09

[a] No endpoint indicated a statistically significant effect of treatment, sex, or the interaction.
[b] Effect sizes shown in bold are considered "large effects".

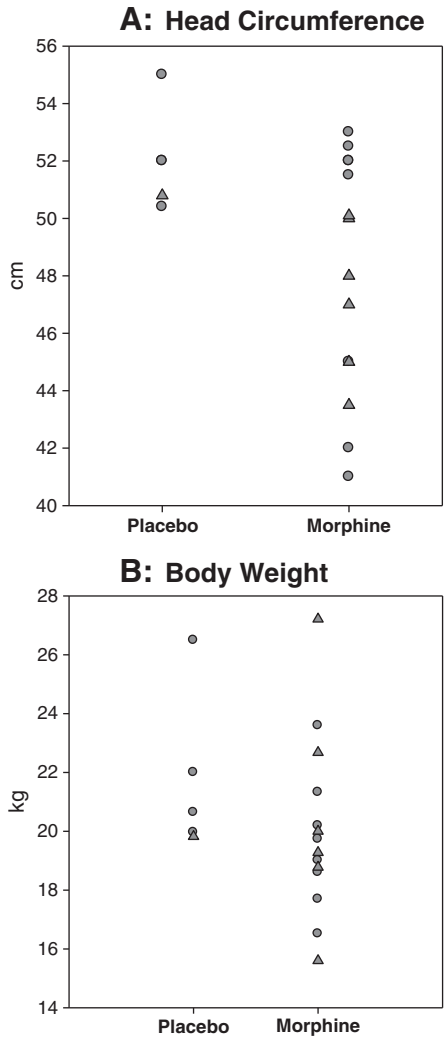

Fig. 1. A. Head circumference (cm) and treatment group. Males are indicated by circle symbols and females as triangles. Cohen's d indicated a large effect size (2.83) for differences in head circumference. Identical circumferences in some subjects caused overlapping data points (2 male subjects in the placebo group with 52 cm circumferences, 2 subjects in the morphine treated group with 45 cm circumferences and 2 male subjects in the morphine treated group with 52 cm circumferences). B. Body weight (kg) and treatment group. Males are indicated by circle symbols and females as triangles. Cohen's d indicated a large effect size (0.81) for differences in body weight.

Behavior Rating Scales, more social problems were apparent in the morphine treated group. These children also exhibited increased latencies to make a choice response in the short-term memory task. That preemptive analgesia had no effects on overall IQ or academic achievement is similar to previous findings of 5–6 year old preterm children who received morphine or other unspecified analgesia in the NICU (de Graaf et al., 2011; MacGregor et al., 1998; Roze et al., 2008). Response latencies have not been previously measured for children who received preemptive analgesia of any type. Thus, although these findings and those of others (MacGregor et al., 1998; Roze et al., 2008) provide increased confidence that preemptive analgesia of preterm infants does not produce severe IQ or academic achievement alterations, the differences in head circumference, body weight, choice response latencies, and social interactions suggest significant differences in these previously unassessed parameters.

Because of the small sample sizes of this study and the potential clinical implications, it is important to emphasize the preliminary nature of these assessments. Until these results are replicated and/or extended, they can only be strongly suggestive. As such, the degree to which the placebo treated group here is representative of preterm infants is very important. Because performance on the neuropsychological tests used here has been measured in previous studies of preterm children, some comparisons can be described. Stanford-Binet full-scale IQ reported here is well within the ranges reported for preterm 3–8 year-old children (Begega et al., 2010; Caravale et al., 2005; Cohen and Parmelee, 1983; Wallace and McCarton, 1997) and extremely low birthweight children at 3 or 5 years of age (Kilbride et al., 2004). The WRAT4 scores here are also within the ranges reported for preterm 8-year-old children (Roberts et al., 2010), small for gestational age 14-year-old adolescents (O'Keeffe et al., 2003), and extremely low birthweight 12–16-year-old adolescents (Saigal et al., 2000). Further, the Vineland Adaptive Behavior Scale adaptive behavior composite score here was within the range of that of preterm 1-year-old infants (Allen et al., 2004). Finally, PR and DMTS performance by the placebo group here was very similar to that previously reported for preterm 6-year-old children (Paule et al., 1999). Thus, despite the small sample size, performance of the placebo group here appears representative of preterm children.

While the neuropsychological performance of the placebo group appears representative of preterm children in general, the small sample size may not be representative or reflective of the larger original Arkansas NEOPAIN cohort. For example, the current study contained only one black subject (5.3% of the total pool) while the original cohort was comprised of 37.5% black subjects, although, it is difficult to speculate on the potential effect of this difference. The current study was underrepresented in placebo subjects at the later gestational age (30–32 weeks), having none in this category while approximately 20% of the placebo group of original cohort was born at 30–32 weeks gestational age. Similarly, the current study was overrepresentated in the morphine treated subjects born at the earliest gestational age (23–26 weeks) relative to that of the original cohort (approximately 42.9% vs. 20.6%, respectively). Given that extremely preterm children can be at increased risk of neuropsychological alterations, such as decreased Stanford–Binet performance, relative to children born at later gestational ages (Dezoete et al., 2003), this increased representation of morphine treated subjects born at the earliest gestational age may have impacted the results. Therefore, it is important that these results be replicated and that followup assessments of increased numbers of subjects in the Arkansas NEOPAIN cohort as well as the other NEOPAIN locations continue.

Measures of body weight and head circumference indicated large effect sizes. Children in the morphine treated group weighed less and had a smaller head circumference than placebo children. As is typical of preterm children (e.g., Bracewell et al., 2008; Kan et al., 2008), the head circumference of the preterm subjects here was much smaller than that of full term children. With the exception of the single placebo girl whose head circumference was at the 25th percentile, all placebo subjects fell at or below the 3rd percentile for full term, same-aged children (see Rollins et al., 2010 for baseline values for children). Nonetheless, preemptive morphine analgesia in the NICU appeared to inhibit head circumference growth and body weight gain. Body weight gain and head circumference growth during time in the NICU (i.e., from birth to discharge) has been reported to be a better predictor of neurodevelopmental outcome at 5 years of age than are growth gains during the next few years (Franz et al., 2009), indicating the sensitivity of this early postpartum period to potential disruption. Franz et al. (Franz et al., 2009) suggest their findings advocate for improving growth in preterm infants via intensive nutritional support in the NICU. If the morphine analgesia used here interfered with nutritional support during this especially vulnerable period, head circumference growth and body weight gain could have been particularly affected. Such a hypothesis appears to be supported by results from the larger NEOPAIN cohort, in which the morphine treated infants achieved full enteral feeds approximately 3 days later than did placebo infants (Menon et al., 2008).

Performance on the PR task indicated similar motivational levels in placebo and morphine treated children; however, the DMTS task

Table 3
Effect size and mean (±SEM) of neuropsychological assessments.

		Placebo		Morphine	
	Cohen's d[a]	Boys	Girls	Boys	Girls
Stanford–Binet		n = 4	n = 1	n = 8	n = 6
Full-scale IQ	−0.04	98.0 ± 5.8	100.0	100.4 ± 2.5	96.7 ± 2.5
Nonverbal IQ	0.06	97.8 ± 6.0	105.0	100.0 ± 2.7	96.7 ± 2.7
Verbal IQ	−0.11	98.8 ± 5.4	95.0	100.3 ± 2.4	97.3 ± 2.8
Fluid reasoning	−0.14	93.3 ± 10.9	100.0	97.0 ± 2.4	96.5 ± 3.4
Knowledge	0.53	97.5 ± 5.5	97.0	91.0 ± 4.9	91.8 ± 2.9
Quantitative reasoning	0.46	102.8 ± 5.7	108.0	100.9 ± 2.0	97.7 ± 2.8
Visual spatial processing	−0.39	99.0 ± 7.2	97.0	105.4 ± 4.2	101.3 ± 3.8
Working memory	−0.17	102.3 ± 6.5	97.0	105.9 ± 2.3	99.5 ± 4.6
WRAT 4		n = 3–4	n = 1	n = 6–8	n = 4–6
Word reading	−0.48	97.8 ± 7.8	104.0	112.0 ± 6.3	99.7 ± 3.1
Sentence comprehension	−0.51	87.0 ± 10.0	77.0	100.3 ± 10.5	89.5 ± 10.2
Spelling	0.24	108.0 ± 2.9	105.0	105.0 ± 3.9	105.8 ± 3.3
Math computation	0.15	99.5 ± 8.5	90.0	97.9 ± 2.6	92.3 ± 3.8
Reading composite	−0.61	91.0 ± 11.6	89.0	108.8 ± 7.7	93.8 ± 8.1
VABS		n = 1–4	n = 1	n = 4–8	n = 3–6
Communication	0.36	114.0 ± 8.0	112.0	105.9 ± 2.5	113.5 ± 7.2
Daily living skills	−0.73	107.0 ± 0.0	93.0	108.0 ± 4.6	110.0 ± 4.7
Socialization	**1.16**	124.0 ± 0.0	–	99.0 ± 9.6	111.3 ± 4.0
Motor skills	−0.21	93.5 ± 9.9	–	95.4 ± 4.9	99.7 ± 5.2
Adaptive behavior composite	**1.03**	117.0 ± 0.0	–	101.3 ± 5.6	112.5 ± 3.7
Maladaptive behavior index	−0.32	15.3 ± 0.8	14.0	15.5 ± 0.6	15.8 ± 1.1
CBCL		n = 4	n = 1	n = 8	n = 6
Internalizing	−0.17	47.3 ± 6.8	39.0	47.1 ± 2.3	47.8 ± 3.3
Externalizing	0.50	49.3 ± 1.9	54.0	44.1 ± 4.8	47.7 ± 2.9
Total problems	0.26	51.3 ± 4.6	45.0	46.9 ± 3.7	48.0 ± 3.7
CCBRS		n = 4	n = 1	n = 8	n = 6
Oppositional	0.11	47.5 ± 2.6	50.0	45.6 ± 3.3	49.3 ± 2.8
Cognitive problems/inattention	0.21	53.0 ± 5.5	44.0	46.8 ± 1.9	52.3 ± 3.5
Hyperactivity	0.13	52.3 ± 5.6	50.0	51.3 ± 2.9	49.8 ± 1.9
Anxious–shy	−0.07	55.8 ± 8.2	45.0	51.3 ± 3.8	59.0 ± 2.6
Perfectionism	−0.59	46.0 ± 2.3	40.0	45.4 ± 2.2	56.5 ± 4.9
Social problems	**−0.83**	45.3 ± 0.3	45.0	47.9 ± 1.8	48.3 ± 1.5
Psychosomatic	0.17	53.3 ± 6.9	43.0	49.6 ± 2.1	48.8 ± 3.5
ADHD index	0.17	51.8 ± 7.2	45.0	46.6 ± 3.1	50.5 ± 3.5
CGI: restless–impulsive	0.24	53.0 ± 7.4	47.0	49.1 ± 2.7	48.8 ± 2.8
CGI: emotional lability	−0.68	41.8 ± 1.5	47.0	45.6 ± 3.2	50.0 ± 2.8
CGI: total	0.08	49.5 ± 5.3	47.0	47.8 ± 3.0	49.0 ± 2.6
DSM-IV: inattentive	0.15	50.5 ± 5.9	42.0	44.9 ± 1.9	50.5 ± 2.8
DSM-IV: hyperactive–impulsive	0.01	53.3 ± 4.8	47.0	52.3 ± 4.3	51.5 ± 3.0
DSM-IV: total	0.09	52.0 ± 5.8	44.0	48.4 ± 3.1	51.0 ± 3.1

[a] Effect sizes shown in bold are considered "large effects"; however, see Section 3.2.2 for additional information.

clearly differentiated the groups. Preterm children have later difficulties in working memory (Clark and Woodward, 2010; Mulder et al., 2011) and attentional delays (Hall et al., 2008), but no study has assessed the effects of neonatal morphine analgesia on these parameters. A large effect size indicated that morphine treated children completed approximately 27% less of the DMTS task than did placebo children. Decreased DMTS task completion could result from a number of factors. Morphine treated children could have experienced more of the 10 s timeouts after an incorrect response, resulting in the presentation of fewer trials in the allotted task time. Average number of incorrect trials was somewhat higher in the morphine treated group, but this does not fully explain the decreased task completion because accuracy did not differ significantly between the two groups. The selection of the delay interval (1–32 s) in the DMTS task is random and if the morphine treated group received more long delay trials, this could have resulted in less task completion; however,

Table 4
Effect size and mean (±SEM) of operant task endpoints.

		Placebo		Morphine	
	Cohen's d[a]	Boys	Girls	Boys	Girls
PR		n = 4	n = 1	n = 7	n = 5
Number of reinforcers earned	−0.12	12.3 ± 1.9	15.0	13.9 ± 1.7	12.7 ± 1.6
DMTS		n = 4	n = 1	n = 6	n = 4
Percent task completed	**0.96**	75.8 ± 4.4	86.7	58.3 ± 7.2	68.3 ± 11.4
Accuracy	0.64	88.9 ± 2.5	97.0	80.1 ± 8.0	86.4 ± 6.1
Observing response latency (s)	−0.37	2.3 ± 0.3	2.4	3.5 ± 0.4	2.4 ± 0.4
Choice response latency (s)[b]	−0.62	2.8 ± 0.3	2.3	4.4 ± 0.4	3.1 ± 0.5
Correct choice response latency (s)[c]	−0.67	2.6 ± 0.2	1.9	4.3 ± 0.6	2.9 ± 0.5
Incorrect choice response latency (s)	0.25	4.3 ± 0.4	10.9	5.7 ± 0.4	4.7 ± 1.1
Number of incorrect trials	−0.37	5.8 ± 1.1	2.0	8.0 ± 2.6	6.5 ± 2.3

[a] Effect sizes shown in bold are considered "large effects".
[b] Choice response latency was longer in the morphine treated group ($p < 0.05$).
[c] Correct choice response latency was longer in the morphine treated group ($p < 0.05$).

both groups each received a nearly identical number of long delay trials (>4 s) (26.4 and 23.5 trials each for the placebo and morphine treated groups, respectively).

More probable is that the morphine treated children completed less of the DMTS task due to their increased choice response latencies. While increased reaction times are typical of preterm children (Pizzo et al., 2010), longer response latencies mean that fewer trials can be completed in the allotted time, resulting in decreased task completion. Response latencies for morphine treated children were longer for both correct and incorrect choices; however, only correct choice response latencies differed significantly between the groups. Because observing response latencies did not differ between the groups, deficits in motoric skills are not likely to explain the choice response latency difference. Increased correct response latencies could indicate that morphine treated children required more time to remember which of the three symbols had been presented as the sample stimulus. Indeed, choice response latencies in children and adults for knowledge-based questions or on a DMTS task are inversely correlated with confidence in the accuracy of the answer (Koriat and Ackerman, 2010; Olsen et al., 2009; Zakay and Tuvia, 1998). Though not assessed here, the morphine treated children may have had less confidence in their choice response. In adults, various brain regions (i.e., portions of the medial temporal lobe, anterior hippocampus, bilateral dorsolateral prefrontal cortex, bilateral fusiform gyri, anterior cingulate cortex and occipital regions) show increased activation during those DMTS delay intervals which are followed by a correct response relative to an those delays followed by an incorrect response (Melrose et al., 2007; Olsen et al., 2009). While it may be tempting to speculate about the potential effects of preemptive morphine analgesia on development of those areas, this requires additional research.

Rather than increased time needed for memory retrieval, an alternative explanation for the increased choice response latencies exhibited by the morphine treated group may involve perceptual reasoning and analysis. Preterm neonates treated with morphine analgesia who were assessed at 5 years of age performed more poorly than placebo children on the visual analysis (also known as Hidden Figures) subtest of the Revised Amsterdam Child Intelligence Test (RAKIT) (de Graaf et al., 2011). The Hidden Figures subtest is thought to measure visual analysis, pattern recognition, matching and the ability to ignore distracting, irrelevant stimuli (Helms-Lorenz et al., 2003). Similarly, the DMTS task involves visual analysis, pattern recognition, and matching. Although the morphine treated children here were no less accurate at this task than were placebo children, the increased latency to respond may indicate the need for increased time to analyze, recognize and match the visual stimulus.

Morphine treated children exhibited approximately 6% higher scores on the social problems scale of the Conners' Comprehensive Behavior Rating Scales, resulting in a large effect size. Seven of the 14 morphine treated children scored as high or higher than the highest scoring placebo child. Items contributing to this measure assess the child's relationships with friends and feelings of inferiority. Deficits in making and maintaining peer relationships could have far-reaching consequences (e.g., Kupersmidt and Patterson, 1991; Schultz et al., 2009). However, social problems as measured by the Child Behavior Checklist were similar in both groups. Items comprising the social problems scale on the Child Behavior Checklist measure the number of friendships and quality of interactions with friends and family. Whether these two scales are significantly correlated is not clear. For example, the social problems scale of the Child Behavior Checklist, but not the same scale of the Conners' Comprehensive Behavior Rating Scales, was able to distinguish between sleep-disordered children and control children (Rosen et al., 2004). Thus, these two scales (social problems in the Child Behavior Checklist and social problems in the Conners' Comprehensive Behavior Rating Scales) could be measuring somewhat different constructs. Similar measures were not assessed in previous studies of the long term effects of preemptive analgesia (MacGregor et al., 1998; Roze et al., 2008). While it is not unusual for formerly preterm children or adolescents to have social problems and/or trouble establishing social contacts (Delobel-Ayoub et al., 2009; Hille et al., 2008; Skranes et al., 2007), a potential worsening of such effects by preemptive morphine analgesia could produce additional problems.

Although it remains to be determined if the increased social problems in morphine treated children are a replicable and/or long-lasting effect, results of laboratory animal research support the existence of such an effect. Play behavior in young rats is one of the earliest forms of social interaction with peers and in many aspects, rodent play behavior resembles the physical play behavior of children. The motivational and rewarding aspects of this behavior appear regulated by CNS opioid systems in that play behaviors can be altered by acute treatment with morphine or opioid antagonists (Jalowiec et al., 1989; Vanderschuren et al., 1995). For example, morphine treatment during the last week of gestation increased play behavior in rats (Hol et al., 1996; Niesink et al., 1999) but early postnatal treatment caused a delay in achieving control levels of play in rats (Najam and Panksepp, 1989). Thus, the alterations in rodent play behavior after morphine treatment may depend on stage of development at treatment. For a translational assessment, it is difficult to determine with any great specificity how comparable the CNS of an early postnatal rat is to a preterm human; however, using certain cortical events as markers, a 11–12 postnatal day old rat may be most similar to a 27 week gestational age human (see www.translatingtime.net and Clancy et al., 2007), which is the average gestational age for the subjects in the current study. Thus, in an extremely general sense and without equating morphine dose or duration of treatment and using previous results (Najam and Panksepp, 1989), it could be predicted that the increased social problems of the morphine treated children may resolve with age.

In summary, while measures of IQ and academic achievement did not differ between the morphine treated and placebo groups, there were indications that preemptive morphine analgesia altered certain morphometrics and behaviors at 5–7 years of age. Morphine treated children had a smaller head circumference, decreased body weight, and exhibited longer choice response latencies in a delayed matching to sample task. Morphine treated children were also described by a parent as having more social problems, an effect specific to creating and maintaining friendships. If these effects prove to be long-lasting, they may interfere with later adolescent functioning. These pilot study results suggest that a larger study with more comprehensive assessments of these key features would enable a more complete description of the relationship between preemptive morphine analgesia in preterm infants and long-term neurocognitive, behavioral, and adaptive outcomes.

Disclaimer

This document has been reviewed in accordance with United States Food and Drug Administration (FDA) policy and approved for publication. Approval does not signify that the contents necessarily reflect the position or opinions of the FDA nor does mention of trade names or commercial products constitute endorsement or recommendation for use. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the FDA.

Conflict of interest

Nothing declared.

Acknowledgements

The authors would like to express their sincere appreciation for the expert technical assistance of Ms. Kris Dudoich and Ms. Sabrina

Maham and we are extremely grateful for the careful and detailed assistance of Ms. Andrea Sutton. Ms. Shari S. Kronsberg, M.S. was invaluable in accessing needed information from the original NEOPAIN study. We are appreciative of the expert administration of the neurocognitive assessments by Kelli Harford, Ph.D., Shari Gaudette, Ph.D. and, Julie Pettapiece Weston, Ph.D. We also acknowledge National Center for Research Resources 020146 (RWH). Portions of this study were supported by the National Center for Toxicological Research/FDA (Experiment # 7243)

References

Allen MC. Neurodevelopmental outcomes of preterm infants. Curr Opin Neurol 2008;21:123–8.
Allen EC, Manuel JC, Legault C, Naughton MJ, Pivor C, O'Shea TM. Perception of child vulnerability among mothers of former premature infants. Pediatrics 2004;113: 267–73.
American Academy of Pediatrics (Committee on Fetus and Newborn; Committee on Drugs; Section on Anesthesiology; and Section on Surgery, Canadian Paediatric Society (Fetus and Newborn Committee. Prevention and management of pain and stress in the neonate. Paediatr Child Health 2000;5:31–47.
American Academy of Pediatrics, Committee on Fetus and Newborn, Committee on Drugs, Section on Anesthesiology, Section on Surgery, Canadian Paediatric Society, Fetus and Newborn Committee. Prevention and management of pain and stress in the neonate. Pediatrics 2000;105:454–61.
American Psychological Association, Publication Manual of the American Psychological Association, Sixth Edition American Psychological Association, 2009.
Anand KJS, Selanikio JD, Group SS. Routine analgesic practices in 109 neonatal intensive care units (NICUs). Pediatr Res 1996;39S:192.
Anand KJ, Hall RW, Desai N, Shephard B, Bergqvist LL, Young TE, Boyle EM, Carbajal R, Bhutani VK, Moore MB, et al. Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial. Lancet 2004;363:1673–82.
Anand KJ, Aranda JV, Berde CB, Buckman S, Capparelli EV, Carlo W, Hummel P, Johnston CC, Lantos J, Tutag-Lehr V, et al. Summary proceedings from the neonatal pain-control group. Pediatrics 2006;117:S9-S22.
Anand KJ, Anderson BJ, Holford NH, Hall RW, Young T, Shephard B, Desai NS, Barton BA. Morphine pharmacokinetics and pharmacodynamics in preterm and term neonates: secondary results from the NEOPAIN trial. Br J Anaesth 2008;101:680–9.
Barker DP, Rutter N. Exposure to invasive procedures in neonatal intensive care unit admissions. Arch Dis Child Fetal Neonatal Ed 1995;72:F47–8.
Begega A, Mendez Lopez M, de Iscar MJ, Cuesta-Izquierdo M, Solis G, Fernandez-Colomer B, Alvarez L, Mendez M, Arias JL. Assessment of the global intelligence and selective cognitive capacities in preterm 8-year-old children. Psicothema 2010;22: 648–53.
Bellu R, de Waal K, Zanini R. Opioids for neonates receiving mechanical ventilation: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2010;95: F241–51.
Bracewell MA, Hennessy EM, Wolke D, Marlow N. The EPICure study: growth and blood pressure at 6 years of age following extremely preterm birth. Arch Dis Child Fetal Neonatal Ed 2008;93:F108–14.
Caravale B, Tozzi C, Albino G, Vicari S. Cognitive development in low risk preterm infants at 3–4 years of life. Arch Dis Child Fetal Neonatal Ed 2005;90:F474–9.
Carbajal R, Rousset A, Danan C, Coquery S, Nolent P, Ducrocq S, Saizou C, Lapillonne A, Granier M, Durand P, et al. Epidemiology and treatment of painful procedures in neonates in intensive care units. JAMA 2008;300:60–70.
Chelonis JJ, Edwards MC, Schulz EG, Baldwin R, Blake DJ, Wenger A, Paule MG. Stimulant medication improves recognition memory in children diagnosed with attention-deficit/hyperactivity disorder. Exp Clin Psychopharmacol 2002;10:400–7.
Chelonis J, Johnson TA, Ferguson SA, Berry KJ, Kubacak B, Edwards MC, Paule MG. Effect of methylphenidate on motivation in children with Attention-Deficit/Hyperactivity Disorder. Exp Clin Psychopharmacol 2011;19:145–153.
Clancy B, Kersh B, Hyde J, Darlington RB, Anand KJ, Finlay BL. Web-based method for translating neurodevelopment from laboratory species to humans. Neuroinformatics 2007;5:79–94.
Clark CA, Woodward LJ. Neonatal cerebral abnormalities and later verbal and visuospatial working memory abilities of children born very preterm. Dev Neuropsychol 2010;35:622–42.
Cohen J. The earth is round ($p < .05$). Am Psychol 1994;49:997-1003.
Cohen SE, Parmelee AH. Prediction of five-year Stanford-Binet scores in preterm infants. Child Dev 1983;54:1242–53.
Colliver JA. Effect-size measures and research in developmental and behavioral pediatrics. J Dev Behav Pediatr 2007;28:145–50.
D'Apolito KC. State of the science: procedural pain management in the neonate. J Perinat Neonatal Nurs 2006;20:56–61.
de Graaf J, van Lingen RA, Simons SH, Anand KJ, Duivenvoorden HJ, Weisglas-Kuperus N, Roofthooft DW, Groot Jebbink LJ, Veenstra RR, Tibboel D, 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: 1391–7.
Delobel-Ayoub M, Arnaud C, White-Koning M, Casper C, Pierrat V, Garel M, Burguet A, Roze JC, Matis J, Picaud JC, et al. Behavioral problems and cognitive performance at 5 years of age after very preterm birth: the EPIPAGE Study. Pediatrics 2009;123: 1485–92.
Dezoete JA, MacArthur BA, Tuck B. Prediction of Bayley and Stanford-Binet scores with a group of very low birthweight children. Child Care Health Dev 2003;29:367–72.
Durlak JA. How to select, calculate, and interpret effect sizes. J Pediatr Psychol 2009;34: 917–28.
Fitzgerald M, Walker SM. Infant pain management: a developmental neurobiological approach. Nat Clin Pract Neurol 2009;5:35–50.
Franz AR, Pohlandt F, Bode H, Mihatsch WA, Sander S, Kron M, Steinmacher J. Intrauterine, early neonatal, and postdischarge growth and neurodevelopmental outcome at 5.4 years in extremely preterm infants after intensive neonatal nutritional support. Pediatrics 2009;123:e101–9.
Hall RW, Boyle E, Young T. Do ventilated neonates require pain management? Semin Perinatol 2007;31:289–97.
Hall RW, Huitt TW, Thapa R, Williams DK, Anand KJ, Garcia-Rill E. Long-term deficits of preterm birth: evidence for arousal and attentional disturbances. Clin Neurophysiol 2008;119:1281–91.
Helms-Lorenz M, Van de Vijver FJR, Poortinga YH. Cross-cultural differences in cognitive performance and Spearman's hypothesis: g or c? Intelligence 2003;31:9-29.
Hille ET, Dorrepaal C, Perenboom R, Gravenhorst JB, Brand R, Verloove-Vanhorick SP. Social lifestyle, risk-taking behavior, and psychopathology in young adults born very preterm or with a very low birthweight. J Pediatr 2008;152:793–800. (800 e1-4).
Hol T, Niesink M, van Ree JM, Spruijt BM. Prenatal exposure to morphine affects juvenile play behavior and adult social behavior in rats. Pharmacol Biochem Behav 1996;55:615–8.
Jalowiec JE, Calcagnetti DJ, Fanselow MS. Suppression of juvenile social behavior requires antagonism of central opioid systems. Pharmacol Biochem Behav 1989;33: 697–700.
Johnston CC, Collinge JM, Henderson SJ, Anand KJ. A cross-sectional survey of pain and pharmacological analgesia in Canadian neonatal intensive care units. Clin J Pain 1997;13:308–12.
Kan E, Roberts G, Anderson PJ, Doyle LW. The association of growth impairment with neurodevelopmental outcome at eight years of age in very preterm children. Early Hum Dev 2008;84:409–16.
Kilbride HW, Thorstad K, Daily DK. Preschool outcome of less than 801-gram preterm infants compared with full-term siblings. Pediatrics 2004;113:742–7.
Koriat A, Ackerman R. Choice latency as a cue for children's subjective confidence in the correctness of their answers. Dev Sci 2010;13:441–53.
Kumar P. Prevention of pain in neonates. JAMA 2008;300:2248.author reply 2248–9.
Kupersmidt JB, Patterson CJ. Childhood peer rejection, aggression, withdrawal, and perceived competence as predictors of self-reported behavior problems in preadolescence. J Abnorm Child Psychol 1991;19:427–49.
MacGregor R, Evans D, Sugden D, Gaussen T, Levene M. Outcome at 5–6 years of prematurely born children who received morphine as neonates. Arch Dis Child Fetal Neonatal Ed 1998;79:F40–3.
Melrose RJ, Poulin RM, Stern CE. An fMRI investigation of the role of the basal ganglia in reasoning. Brain Res 2007;1142:146–58.
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:F362–7.
Mulder H, Pitchford NJ, Marlow N. Inattentive behaviour is associated with poor working memory and slow processing speed in very preterm children in middle childhood. Br J Educ Psychol 2011;18:147–60.
Najam N, Panksepp J. Effect of chronic neonatal morphine and naloxone on sensorimotor and social development of young rats. Pharmacol Biochem Behav 1989;33: 539–44.
Niesink RJ, van Buren-van Duinkerken L, van Ree JM. Social behavior of juvenile rats after in utero exposure to morphine: dose-time-effect relationship. Neuropharmacology 1999;38:1207–23.
O'Keeffe MJ, O'Callaghan M, Williams GM, Najman JM, Bor W. Learning, cognitive, and attentional problems in adolescents born small for gestational age. Pediatrics 2003;112:301–7.
Olsen RK, Nichols EA, Chen J, Hunt JF, Glover GH, Gabrieli JD, Wagner AD. Performance-related sustained and anticipatory activity in human medial temporal lobe during delayed match-to-sample. J Neurosci 2009;29:11880–90.
Paule MG, Cranmer JM, Wilkins JD, Stern HP, Hoffman EL. Quantitation of complex brain function in children: preliminary evaluation using a nonhuman primate behavioral test battery. Neurotoxicology 1988;9:367–78.
Paule MG, Chelonis JJ, Buffalo EA, Blake DJ, Casey PH. Operant test battery performance in children: correlation with IQ. Neurotoxicol Teratol 1999;21:223–30.
Pizzo R, Urben S, V.D.L. M, Borradori-Tolsa C, Freschi M, Forcada-Guex M, Huppi P, Barisnikov K. Attentional networks efficiency in preterm children. J Int Neuropsychol Soc 2010;16:130–7.
Porter FL, Anand KJS. Epidemiology of pain in neonates. Res Clin Forums 1998;20:9-16.
Quinn MW, Otoo F, Rushforth JA, Dean HG, Puntis JW, Wild J, Levene MI. Effect of morphine and pancuronium on the stress response in ventilated preterm infants. Early Hum Dev 1992;30:241–8.
Quinn MW, Wild J, Dean HG, Hartley R, Rushforth JA, Puntis JW, Levene MI. Randomised double-blind controlled trial of effect of morphine on catecholamine concentrations in ventilated pre-term babies. Lancet 1993;342:324–7.
Roberts G, Anderson PJ, Davis N, De Luca C, Cheong J, Doyle LW. Developmental coordination disorder in geographic cohorts of 8-year-old children born extremely preterm or extremely low birthweight in the 1990s. Dev Med Child Neurol 2010;53: 55–60.
Rollins JD, Collins JS, Holden KR. United States head circumference growth reference charts: birth to 21 years. J Pediatr 2010;156:907–13. (913 e1-2).

Rosen CL, Storfer-Isser A, Taylor HG, Kirchner HL, Emancipator JL, Redline S. Increased behavioral morbidity in school-aged children with sleep-disordered breathing. Pediatrics 2004;114:1640–8.
Roze JC, Denizot S, Carbajal R, Ancel PY, Kaminski M, Arnaud C, Truffert P, Marret S, Matis J, Thiriez G, et al. Prolonged sedation and/or analgesia and 5-year neurodevelopment outcome in very preterm infants: results from the EPIPAGE cohort. Arch Pediatr Adolesc Med 2008;162:728–33.
Saigal S, Hoult LA, Streiner DL, Stoskopf BL, Rosenbaum PL. School difficulties at adolescence in a regional cohort of children who were extremely low birth weight. Pediatrics 2000;105:325–31.
Schultz D, Tharp-Taylor S, Haviland A, Jaycox L. The relationship between protective factors and outcomes for children investigated for maltreatment. Child Abuse Negl 2009;33:684–98.
Simons SH, van Dijk M, Anand KS, Roofthooft D, van Lingen RA, Tibboel D. Do we still hurt newborn babies? A prospective study of procedural pain and analgesia in neonates. Arch Pediatr Adolesc Med 2003;157:1058–64.
Skranes J, Vangberg TR, Kulseng S, Indredavik MS, Evensen KA, Martinussen M, Dale AM, Haraldseth O, Brubakk AM. Clinical findings and white matter abnormalities seen on diffusion tensor imaging in adolescents with very low birth weight. Brain 2007;130:654–66.
Thompson B. Journal editorial policies regarding statistical significance tests: Heat is to fire as p is to importance. Educ Psychol Rev 1999;11:157–69.
Vanderschuren LJ, Spruijt BM, Hol T, Niesink RJ, Van Ree JM. Sequential analysis of social play behavior in juvenile rats: effects of morphine. Behav Brain Res 1995;72:89–95.
Wallace IF, McCarton CM. Neurodevelopmental outcomes of the premature, small-for-gestational-age infant through age 6. Clin Obstet Gynecol 1997;40:843–52.
Zakay D, Tuvia R. Choice latency times as determinants of post-decisional confidence. Acta Psychol 1998;98:103–15.
Zakzanis KK. Statistics to tell the truth, the whole truth, and nothing but the truth: formulae, illustrative numerical examples, and heuristic interpretation of effect size analyses for neuropsychological researchers. Arch Clin Neuropsychol 2001;16:653–67.