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Complementary, Holistic, and Integrative Medicine: Therapies for Neurodevelopment in Preterm Infants

Elaine Galicia-Connolly, MD,* Larissa Shamseer, MSc,* Sunita Vohra, MD, MSc*

Author Disclosure
Drs Galicia-Connolly and Shamseer have disclosed no financial relationships relevant to this article. Dr Vohra receives salary support from the Alberta Heritage Foundation for Medical Research. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Background
Preterm birth is defined as birth occurring at age <37 weeks, with extremely preterm birth occurring at <26 weeks. (1) Children born prematurely have been shown to have significantly lower cognitive scores compared with children born at term by age 5 years, with scores being significantly positively correlated to both birthweight and gestational age. (2) In addition, preterm children are significantly more likely to develop attention deficit hyperactivity disorder and other behavioral problems at school age than children born at term.

Complementary and alternative medicine therapies are used to help alleviate long-term consequences of preterm birth. In this article, we review commonly used complementary and alternative medicine therapies (long-chain polyunsaturated fatty acid [LCPUFA] supplementation, massage therapy, and music therapy) and their effects on the neurodevelopment of preterm infants.

Search Strategy
The following electronic bibliographic databases were searched: MEDLINE, EMBASE, Cochrane’s Database of Systematic Reviews and Register of Controlled Trials (CENTRAL), and PsycInfo. The search was limited to systematic reviews and clinical trials. Search terminology included neurodevelopment, premature infant, nutritional supplementation, massage therapy, music therapy, and their respective synonyms according to database. No language limits were imposed. Included studies were restricted to clinical studies.

Results
Long-chain Polyunsaturated Fatty Acids
The n-3 LCPUFA, docosahexanoic acid (DHA), is a major brain lipid believed to play a role in brain development. It is thought that preterm infants may receive less DHA than full-term infants due to a shortened third trimester. (3)(4)

A systematic review included 32 randomized controlled trials (RCTs) of which 10 studies were meta-analyzed. The RCTs examined the effect of enteral feeds of LCPUFA-supplemented formulas on neurodevelopment and diseases associated with prematurity in premature infants. (5) By using the Bayley Scales of Infant Development, which measures three components of neurodevelopment (cognitive, motor, and behavioral functioning), the authors found no significant differences between groups.

Although supplemented infants scored an average of 3.4 points higher than controls in cognitive development (weighted mean difference [WMD]: 3.44 [95% confidence interval (CI): 0.56–6.31]; \( P = .02; n = 879 \)), the authors concluded that this difference was mainly attributable to two trials with large effect sizes and wide CIs. Psychomotor development was significantly lower in supplemented infants than controls (WMD: −7.99 [95% CI: −14 to −1.99]; \( P = .009; n = 87 \)).

Abbreviations
- CCT: controlled clinical trial
- CI: confidence interval
- DHA: docosahexanoic acid
- fVEP: flash visual evoked potential
- IQR: interquartile range
- LBW: low birthweight
- LCPUFA: long-chain polyunsaturated fatty acid
- MDI: Mental Developmental Index
- RCT: randomized controlled trial
- WMD: weighted mean difference

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A Cochrane systematic review identified 19 RCTs that assessed the effects of LCPUFA formulas on the visual development, general development, and growth of preterm infants. (6) Pooled data from 15 RCTs did not indicate any long-term benefits of LCPUFA supplementation over control for any of these outcomes.

An RCT, published after the two preceding systematic reviews, compared supplementation of high-dose DHA (≈1% total fatty acids) to standard-dose DHA (≈0.3% total fatty acids) in premature infants (<33 weeks). (7) Six hundred fifty-seven infants were randomly assigned to receive either treatment. If infants were breastfed, mothers were asked to take a supplement containing either DHA or placebo (because human milk contains a base level of DHA) to achieve human milk concentrations of 1% or 0.3% DHA, respectively. If infants were fed formula, they were given either high-dose or low-dose DHA formula to achieve the same DHA levels as above. Infants received the intervention two to four times per day until their expected delivery date.

The Mental Developmental Index (MDI) of the Bayley Scales of Infant Development (BSID-II) at corrected age 18 months was chosen as the primary outcome. The authors did not find any difference in the MDI scores between groups (mean difference, 1.9 points [95% CI: −1.0 to 4.7]), but after stratifying by gender, the study revealed that girls on high dose supplementation had a significantly higher score than those on standard dose (adjusted mean difference, 4.5 [95% CI: 0.5–8.5]); no such difference was found among boys. They postulated that this difference between genders may be due to the higher rate of endogenous synthesis of DHA from its precursor fatty acid, α-linoleic acid, in girls over boys. There was no significant difference in adverse clinical outcomes between groups. This study provides evidence that gender may be a potential confounder and that higher doses of DHA supplementation may be beneficial for improving mental development, at least in girls. No harms were found with high-dose DHA supplementation.

**Massage**

Underlying neurobiologic mechanisms of the effects of massage are poorly understood, but it is postulated to involve mechanisms that increase insulin, insulin growth factor, vagal activity, and gastric motility. (8)

A Cochrane systematic review included 14 RCTs that compared systematic tactile stimulation (consisting of massage or “still gentle touch”) versus standard care in preterm (<37 weeks) and low birthweight (LBW; <2500 g or 5.5 lb) infants. (9) Primary outcomes of the review were weight gain and length of stay; developmental and behavioral outcomes were measured by using the Brazelton Scale or the Bayley scale.

Infants who received massage experience gained clinically insignificantly more weight (WMD, 5.1 g [95% CI: 3.5–6.7]), had a 4.5-day (95% CI: 2.4–6.5) shorter length of stay in hospital, but showed unclear benefits in subscales of the Brazelton scale. Studies were found to be highly heterogeneous, and an analytic approach to account for such differences revealed that massage was significantly better than routine care in one subscale: motor maturity (WMD, 0.85 [95% CI: 0.17–1.53]). Methodologic concerns about blinding and selective reporting of some outcomes in included studies of this review may diminish the credibility of its findings.

A controlled clinical trial (CCT) conducted in Russia evaluated the effects of massage given from age 2 months to 8 months. (10) The group exposed to massage were 40 LBW infants (<2.5 kg birthweight), 90% of whom were premature. The unexposed group was 40 LBW infants matched for age, gender, gestational age, birthweight, and geographic distribution. The Minnesota Infant Development Inventory was used to assess social, self-help, gross motor, fine motor, and language skills. Authors reported significant improvement in favor of massage in all five areas.

To determine whether massage accelerates brain development, a CCT in Italy evaluated the effects of three daily massages lasting 15 minutes each over a period of 10 days in 10-day-old infants (±1 day). (11) Ten healthy preterm infants of gestational age 30 to 33 weeks received massage and were compared with 10 similarly aged, gender- and birthweight-matched infants. The authors studied electrophysiologic outcomes (EEG, flash visual evoked potentials [fVEPs], and brainstem auditory evoked potentials) as an index of brain maturation. Behavioral acuity was assessed by using the Bébé Vision Tropique acuity card procedure. Both massaged and control infants were exposed to classical music (Johannes Brahms’ Wiegenlied) diffused in the environment in the daytime.

The authors found an increase in EEG maturation after 3 weeks, as evidenced by transition from discontinuous to continuous activity with a progressive reduction of the duration of intervals between bursts of activity. There was a significant reduction (Mann–Whitney U test; P = 0.011; n = 10 for both groups; Cohen d = 1.33) in maximum interburst interval in massaged infants (7 seconds, interquartile range [IQR] = 5.3–9) compared with control infants (2.8 seconds, IQR = 2–3.8). N300, the most prominent peak of fVEPs, normally reveals progressive lengthening during the first months after birth. N300 latency measured before and after treatment revealed a significantly larger reduction in the massaged infants.
than in the control group (Mann–Whitney U test $P = .013$; $n = 10$ in both groups; Cohen $d = 1.4$). These differences were not evident at 7 and 12 months of observation. No acceleration was seen in the brainstem auditory evoked potentials. Visual acuity at 3 months’ postterm was significantly better in massaged infants than in controls ($t$ test, $P < .001$, Cohen $d = 2.2$, $n = 10$ for both groups).

**Music**

A systematic review and meta-analysis evaluated the effects of music on physiologic parameters and length of hospital stay in premature infants. (12) Ten studies of unclear design were included, four of which were conducted by review authors. The authors report the overall size ($d$) for all measured outcomes between the music and nonmusic groups in all studies to be 0.8268 (95% CI: 0.68–0.97). Although this analysis demonstrates a large and significant effect size, methods of meta-analysis of the review were not described, nor is combining effects across outcomes a typical approach to meta-analysis. Because it is unclear how the authors arrived at their conclusions and effect size estimates and the combined treatment effects for each outcome were not presented, it is difficult to draw any valid conclusions from the findings.

**Adverse Events**

Only four of the seven studies (57%) included in this review article revealed adverse events; none revealed any increase in the number of adverse events in the intervention versus the control arm. In a narrative review, Heird (13) examined the safety of the use of PUFAs in neonates. Theoretical concerns would be lower birthweights, increased risk of oxidant damage (ie, necrotizing enterocolitis, bronchopulmonary dysplasia, and retrolental fibroplasia), altered eicosanoid metabolism, and possible gene transcription defects. However, there were no significant differences in the risk of adverse clinical outcomes between supplemented and control groups in data derived from two systematic reviews and a large multicenter trial involving a total of 4,555 infants. (5)(6)(7)

Vickers et al (9) reported no adverse effects of touch or massage in their systematic review on massage. Kelmanson and Adulas (10) and Guzzetta et al (11) did not comment on adverse events of massage in their preterm subjects. A systematic review on the safety of massage in children revealed that, overall, massage therapy is safe. (14) The majority of adverse events were mild, including local pain or swelling, mild fevers, and skin rashes. The few moderate or severe adverse events reported involve people untrained in massage. Newborn abdominal massage was associated with seven cases of intestinal volvulus in preterm infants who received massage from allied health personnel; abdominal massage in premature newborns by untrained providers should be avoided until investigated further.

**Acknowledgments.** The authors thank the invaluable assistance of Connie Winther and Soleil Surette in the literature search for this article.

**Summary**

- Limited but positive findings have been reported for massage therapy and music in preterm neurodevelopment, whereas long-chain polyunsaturated fatty acids present contradictory evidence with some trial data revealing gender effects. Further studies involving well-controlled or sham trials with definite end points would be helpful.
- Overall, in trained hands, these therapies seem to be safe in children.

**Note:** To view a table summarizing the studies discussed in this article and to view the references for this article, visit [http://pedsinreview.aappublications.org](http://pedsinreview.aappublications.org) and click on the article title.
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References
### Polyunsaturated Fatty Acids (PUFAs)

<table>
<thead>
<tr>
<th>Author (Reference No.)</th>
<th>Design</th>
<th>Population and Outcomes of Interest</th>
<th>Intervention (Dose, Frequency, Duration)</th>
<th>Efficacy and Safety (Primary and Secondary Outcomes with $P$ Values and Confidence Interval CI)</th>
<th>Critical Appraisal of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smithers et al 2008 (5)</td>
<td>Cochrane systematic review and meta-analysis</td>
<td>10 randomized controlled trials (RCTs) examining disease risk and neurodevelopment of healthy preterm infants (&lt;37 wk gestational age) for a total of 1,688 infants</td>
<td>n-3 ± n-6 long-chain polyunsaturated fatty acid (LCPUFA) supplemented formula given for ≥1 mo compared with standard preterm formula containing no LCPUFAs</td>
<td>No differences in Bayley Scales of Infant Development between groups</td>
<td>Results on psychomotor development limited by small sample size</td>
</tr>
<tr>
<td>Simmer et al 2009 (6)</td>
<td>Cochrane systematic review and meta-analysis</td>
<td>15 RCTs examining growth, visual development, and general development in preterm infants fed LCPUFA-supplemented formula in preterm infants (&lt;37 wk gestational age) for a total of 2,355 infants</td>
<td>Formulas supplemented with n-3 and n-6 LCPUFAs</td>
<td>No significant differences in any visual assessment between supplemented and control infants</td>
<td>No significant effect of supplementation on neurodevelopment</td>
</tr>
</tbody>
</table>

Inconsistent results on benefits of supplementation on growth (4/13 studies revealed benefits at different postnatal ages); weight and length (five studies revealed benefit from supplementation at 2 mo postterm, but four studies revealed no significant effect at 12 mo [four studies, $N = 271$] and 18 mo [two studies, $N = 396$] postterm)
<table>
<thead>
<tr>
<th>Author (Reference No.)</th>
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<th>Population and Outcomes of Interest</th>
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<th>Efficacy and Safety&lt;sup&gt;a&lt;/sup&gt; (Primary and Secondary Outcomes with P Values and Confidence Interval [CI])</th>
<th>Critical Appraisal of Study</th>
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</thead>
<tbody>
<tr>
<td>Makrides et al 2009 (7)</td>
<td>Multicenter (five Australian hospitals) double blind RCT</td>
<td>Healthy preterm infants (&lt;33 wk), followed up until 18 mo, N = 657 infants randomly assigned</td>
<td>High docosahexanoic acid (DHA) (~1% total fatty acids) enteral feeds by administering six 500-mg DHA-rich tuna capsules to lactating mothers allocated to high DHA to achieve 1% total fatty acids in their human milk versus standard DHA (~0.3% total fatty acids) enteral feeds by administering six 500-mg placebo soy capsules that did not change fat content or fatty acid composition of their human milk given from age 2 to 4 days until term corrected age. Note: If supplementary formula was required, infants were given either high DHA preterm formula (~1% DHA and 0.6% arachidonic acid [AA]) or standard preterm infant formula (~0.35% DHA and 0.6% AA)</td>
<td>Bayley Mental Developmental Index (MDI) scores did not differ between the high- and standard-DHA groups (mean difference, 1.9 [95% CI: −1.0 to 4.7]) MDI scores among girls fed high DHA diet higher than girls fed standard DHA diet (unadjusted mean difference, 4.7 [95% CI: 0.5–8.8]; adjusted mean difference, 4.5 [95% CI: 0.5–8.5]), but no differences between groups in MDI scores among boys For infants born &lt;1,250 g, MDI in the high DHA group was higher than with standard DHA but was not statistically significant; for infants ≥1,250 g, there was no difference between treatment groups. Psychomotor Development Index scores did not differ between groups (mean difference, 0.9 [95% CI: −1.8 to 3.6])</td>
<td>Dropout rate 6.5%. Gender effects identified post hoc. Explored effects of higher doses of DHA supplementation</td>
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<sup>a</sup> No significant effect on bleeding time and red cell membrane fragility; no evidence of impaired growth
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<tr>
<td>Vickers et al 2009 (9)</td>
<td>Cochrane systematic review and meta-analysis</td>
<td>$N = 14$ RCTs where infants with gestational age $&lt; 37$ wk or weight at $&lt; 2500$ g received systematic tactile stimulation with at least one outcome measuring weight gain, length of stay, behavior, and development in a total of 512 infants</td>
<td>Massage experience (infants rubbed or stroked for $\sim 15$ min three to four times a day) for 5–10 d in most studies, some including “still, gentle touch” where hands placed gently on them for 15–20 minutes as they slept, with no stroking or rubbing motions applied by nurses in some studies versus standard care</td>
<td>Primary outcomes: weight gain and length of stay. Secondary outcomes: developmental and behavioral outcomes by using Brazelton and Bayley scales. Massage intervention effects on the Brazelton scale 1. Slightly improved performance for habituation (weighted mean difference [WMD], 0.8 [95% CI: 0.5–1.1]), motor maturity (WMD, 0.8 [95% CI: 0.5–1.1]), and range of state (WMD, 0.6 [95% CI: 0.2–0.9]), but differences between groups not statistically significant when random effects model used 2. Improved performance on orientation (WMD, 0.5 [95% CI: 0–1]) and state regulation (WMD, 0.5 [95% CI: −0.1 to 1.0]) had lower confidence limits approach the line of no difference 3. No evidence of effect found on autonomic stability (WMD, −0.1 [95% CI: 0.6–0.3]) or on number of abnormal reflexes (WMD, −0.6 [95% CI: −1.6 to 0.4])</td>
<td>Excluded trials that did not have random allocation, uncontrolled allocation and crossover trials Authors cited that most trial reports did not describe any withdrawals or dropouts, had potential problems in performance bias, blinding in length of stay, and reporting bias Authors analyzed massage and still gentle touch separately No report on cost-effectiveness</td>
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Critical requirement for oxygen therapy at 36 wk than infants fed standard practice.
<table>
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| Guzetta et al 2009 (11) | Controlled clinical trial (CCT) | $N = 10$, healthy preterm infants (gestational age 30–33 wk) versus $N = 10$ age-, gender-, and birthweight-matched controls | 10 d of 15-min massage sessions given three times a day, with a 2-d period of rest after the fifth day, administered on day 10 ($\pm 1$) after birth | 1. Electrophysiologic measures:  
(a) EEG: increased maturation in the EEG after 3 wk as evidenced by transition from discontinuous to continuous activity with a progressive reduction of the duration of intervals between bursts of activity. There was a significant reduction (Mann–Whitney $U$ test $P = 0.011$; $n = 10$ for both groups, Cohen $d = 1.33$) in maximum interburst interval in massaged infants (7 s, interquartile range [IQR] = 5.3–9) compared with control infants (2.8 s, IQR = 2–3.8).  
(b) Flash visual evoked potentials (fVEPs): N300 latency measured before and after treatment revealed a significantly larger reduction in the massaged infants (median reduction 42.8 ms, IQR = 25.1–63.5) than in the control group (median reduction 10.8 ms, IQR = 4–24.2; Mann–Whitney | No adverse effects of touch or massage occurred in any of the studies  
No randomization before group assignment  
Electrophysiologic assessment of outcomes were limited at 3 wk; assessed offline by an examiner blinded to group assignment |
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<tr>
<td>Kelmanson, Adulas 2009 (10)</td>
<td>CCT</td>
<td>$N = 40$ healthy LBW infants ($&lt;2.5$ kg at birth), with $90%$ ($n = 36$) LBW preterm ($\leq 36$ wk) and $10%$ ($n = 4$) LBW but term infants versus $N = 40$ healthy LBW gender-, gestational age-, weight at birth-, date of birth-, and geographically matched controls</td>
<td>Regular massage (frequency and dose details not given) from age 2 mo until 8 mo (total 6 mo duration)</td>
<td>Massage group had significantly better language, gross motor, fine motor, and social skills on all monthly assessments compared with the control group (all $P$ values $\leq 0.05$, no CI given), despite adjustment for confounders (gender, gestational age, Apgar scores, respiratory distress at birth, feeding patterns, birthweight, maternal age, maternal smoking during pregnancy, birth order, maternal education, marital status, and simultaneous influence of abovementioned variables). Reported no violations of protocol, refusal to participate, or losses to follow-up</td>
<td>No randomization. No blinding. No assessment of long-term effects of massage. No reporting of adverse events</td>
</tr>
<tr>
<td>Author (Reference No.)</td>
<td>Design</td>
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<tr>
<td>Standley 2002 (12)</td>
<td>Systematic review and meta-analysis</td>
<td>10 experimental studies on premature and LBW infants evaluating music as a separate independent variable, with N = 780 infants</td>
<td>Music</td>
<td>Dependent variables studied were as follows: observed behavioral rate, heart rate, respiration rate, oxygen saturation level, days in hospital, weight gain, behavioral state, feeding rate, and nonnutritive sucking rate had effect sizes ranging from 0.4915 to 1.9528. Overall effect size, $d = 0.8268$, 95% CI: 0.68–0.97</td>
<td>Unspecified degree of prematurity; Limited literature search; majority of included studies (60%) were self-authored; No information on study designs of included studies; No information on adverse events</td>
</tr>
</tbody>
</table>

AA=arachidonic acid; CCT=controlled clinical trial; CI=confidence interval; DHA=docosahexanoic acid; fVEP=flash visual evoked potential; IQR=interquartile range; LBW=low birthweight; LCPUFA=long-chain polyunsaturated fatty acid; RCT=randomized controlled trial; WMD=weighted mean difference.