# Effect of Chelation Therapy on the Neuropsychological and Behavioral Development of Lead-Exposed Children After School Entry

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**ABSTRACT.** *Objective.* **Some children in the United States continue to be exposed to levels of lead that increase their risk for lowered intellectual functioning and behavior problems. It is unclear whether chelation therapy can prevent or reverse the neurodevelopmental sequelae of lead toxicity. The objective of this study was to determine whether chelation therapy with succimer (dimercaptosuccinic acid) in children with referral blood lead levels between 20 and 44 μg/dL (0.96-2.12 μmol/L) at 12 to 33 months of age has neurodevelopmental benefits at age 7 years.**

*Methods.* **The Treatment of Lead-Exposed Children (TLC) study is a randomized, double-blind, placebo-controlled trial that was conducted between September 1994 and June 2003 in Philadelphia, PA; Newark, NJ; Cincinnati, OH; and Baltimore, MD. Of 1854 referred children who were between the ages of 12 to 33 months and screened for eligibility, 780 were randomized to the active drug and placebo groups stratified by clinical center, body surface area, blood lead level, and language spoken at home. At 7 years of age, 647 subjects remained in the study. Participants were randomly assigned to receive oral succimer or placebo. Up to 3 26-day courses of succimer or placebo therapy were administered depending on response to treatment in those who were given active drug. Eighty-nine percent had finished treatment by 6 months, with all children finishing by 13 months after randomization. All participants received residential lead hazard control measures before treatment. TLC subjects also received a daily multivitamin supplement before and after treatment(s) with succimer or placebo. Scores on standardized neuropsychological measures that tap cognition, behavior, learning and memory, attention, and neuromotor skills were measured.**

*Results.* **Chelation therapy with succimer lowered average blood lead levels for ~6 months but resulted in no benefit in cognitive, behavioral, and neuromotor endpoints.**

*Conclusion.* **These new follow-up data confirm our previous finding that the TLC regimen of chelation therapy is not associated with neurodevelopmental benefits in children with blood lead levels between 20 and 44 μg/dL (0.96–2.17 μmol/L). These results emphasize the importance of taking environmental measures to prevent exposure to lead. Chelation therapy with succimer cannot be recommended for children with blood lead levels between 20 and 44 μg/dL (0.96–2.12 μmol/L).** ***Pediatrics* 2004;114:19–26;** ***child, lead, environmental exposure, chelation therapy, succimer, cognition, clinical trials.***

ABBREVIATIONS. CDC, Centers for Disease Control and Prevention; TLC, Treatment of Lead-Exposed Children; NEPSY, Developmental Neuropsychological Assessment; CI, confidence interval.

Before the availability of chelating drugs, as many as 45% of lead-poisoned children who presented with signs or symptoms of encephalopathy died, and more than one quarter of surviving patients experienced severe neurologic sequelae.[1–3] Cases of this nature are now extremely rare, and the concern with lead toxicity in US children has shifted from symptomatic lead poisoning to subclinical effects. Blood lead levels in US children have declined dramatically over the past 2 decades.[4,5] However, blood lead concentrations of 10 μg/dL (0.48 μmol/L) and lower have been associated with decreased scores on psychometric tests designed for children.[6,7]

In 1991, the Food and Drug Administration licensed succimer (dimercaptosuccinic acid) for the oral chelation of lead in children with blood lead levels at or above 45 μg/dL (2.17 μmol/L).[8] In the same year, the United States Centers for Disease Control and Prevention (CDC) reduced the action threshold from a blood lead concentration of 25 μg/dL (1.2 μmol/L) to 10 μg/dL (0.48 μmol/L).[9] This recommendation was based on epidemiologic studies reporting cognitive impairments at blood lead levels below 25 μg/dL (1.2 μmol/L). Nevertheless, the CDC made no specific recommendations about chelation therapy of children with blood lead levels below 45 μg/dL. Although succimer reduced

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blood lead concentration in exposed children,[10] the effects of treatment on cognitive status were unknown. Thus, in 1994, we initiated a multicenter, randomized, placebo-controlled clinical trial of succimer. The Treatment of Lead-Exposed Children (TLC) trial was designed to test the hypothesis that children who had moderately elevated blood lead concentrations and were given succimer would attain higher scores on standardized tests of neurodevelopment than children who were given placebo.[11,12]

Three years after randomization, no salutary effects of treatment with succimer were observed on a battery of neuropsychological tests administered to TLC subjects when they were, on average, 5 years of age. These included measures of IQ, attention, language, sensorimotor acuities, visuospatial skills, memory, and behavioral problems.[13] We could not attribute the failure to find differences to drug dose or lack of compliance with the TLC regimen. We concluded that because lead poisoning and its effects on neurodevelopment are entirely preventable, our inability to demonstrate effective treatment lent additional support to efforts to protect children from exposure to lead.

Because there were no detectable effects of pharmacologic treatment on neurodevelopment, we combined the 2 treatment arms in an analysis of the relationship between the rate of decline in blood lead levels and improvements in cognition.[14] This ancillary analysis was inspired by an earlier observational study in New York of children who were 1 to 7 years of age and had blood lead levels between 25 and 55 $\mu$g/dL (1.2–2.6 $\mu$mol/L).[15] In the New York study, children who were given ethylenediaminetetraacetic acid and/or therapeutic iron when clinically indicated were followed for 6 months. Regardless of the therapeutic regimen, children whose blood lead level fell the most had the largest improvement in cognitive test scores. In TLC, the change in cognitive test scores between the baseline and 3-year follow-up was also correlated with decline in blood lead concentration. However, a closer examination of the data revealed that this was attributable only to an association in the placebo group. No relationship was observed between falling blood lead levels and improved cognition in the group that was treated with active drug. We concluded that the overall increase in cognitive attainment could not be attributable to the effects of treatment on blood lead concentrations.[14]

Although results of the first wave of follow-up for TLC were consistently negative for drug effects on cognition and behavior, they were not necessarily conclusive. Lead may affect higher level neurocognitive processes that are inaccessible, difficult to assess, or absent in the preschool-aged child. In older children, a wider and more differentiated range of abilities can be examined, scores on psychometric measures are more precise and reliable, and early academic performance and social functioning outside the home environment can be evaluated. Therefore, we followed the cohort into the first years of elementary education to determine whether these later emerging neurodevelopmental functions were spared the effects of lead in treated children compared with placebo control subjects.

## METHODS

### Study Population

The TLC study was approved by the institutional review boards at the clinical sites, data coordinating center, the CDC, and the National Institute for Environmental Health Sciences. The TLC clinical sites were Philadelphia, PA; Newark, NJ; Cincinnati, OH; and Baltimore, MD. Parents or guardians signed informed consent documents covering 3 phases of the study, including all activities leading up to randomization (if qualified), and for later follow-up studies as described in this report. Methods are presented in detail elsewhere.[11] We accepted referral of children who were 12 to 33 months of age, had blood lead levels between 20 and 44 $\mu$g/dL (0.96–2.12 $\mu$mol/L), and could be tested in English or Spanish (Newark site only). We measured blood lead concentration in a venous sample and inspected the child's home to determine whether cleaning and minor repair could be expected to suppress additional exposure to lead dust. Each family was given a month's supply of TLC vitamin and mineral supplements that included iron, zinc, calcium, and copper. Children who had confirmed venous blood lead concentrations between 20 and 44 $\mu$g/dL (0.96–2.12 $\mu$mol/L) and lived in cleanable housing had a second visit. The child was randomized when a second venous blood lead level was also between 20 and 44 $\mu$g/dL (0.96–2.12 $\mu$mol/L). We cleaned the child's home with a high-efficiency particle arrestor vacuum, damp mopped or wiped with a trisodium phosphate solution, and performed minor carpentry when necessary and paint stabilization.

### Study Protocol

Between 1994 and 1997, the data coordinating center at the Harvard School of Public Health randomized 780 children: 396 to succimer and 384 to placebo. Vitamin and mineral supplements were discontinued once the child was assigned to a treatment group, prescribed again after the treatment period, and continued through follow-up. Treatment assignments were randomized within strata of clinical center, body surface area, baseline blood lead level, and Spanish language. McNeil Consumer Products provided 100-mg unmarked succimer (dimercaptosuccinic acid) and placebo capsules of identical appearance. Because succimer has a strong, sulfurous, mercaptan odor, we packed 200 mg of succimer in a vented plastic cylinder in each bottle of placebo and succimer. Courses of therapy were 26 days and aimed to provide 1050 mg/M$^2$/day for the first 7 days and then 700 mg/M$^2$/day thereafter.[12]

Children could receive up to 3 courses of drug or placebo. TLC patients were scheduled to return for clinic visits at 7, 28, and 42 days after the beginning of each treatment course. When a child who was receiving succimer had a blood lead level of $\geq$15 $\mu$g/dL (0.72 $\mu$mol/L) at the 6- to 8-week follow-up visit of the first or second course (median: 48 days; 95% range: 41–101 days for the first course, similar for the second), an additional course of treatment was initiated. Of all children who were given succimer, 83% required a second course, and 83% of those who received a second course required a third. Eighty-nine percent had finished treatment by 6 months, with all children finishing by 13 months after randomization. Children who were given placebo were assigned to re-treatment to match the frequency of re-treatment of children who were given succimer within the strata used for initial randomization. By parental report, >90% of doses were given, and, by pill count, ~76% of the capsules were gone from the bottle. Twenty-six percent of caregivers who were giving placebo and 40% of families who were giving succimer reported difficulty administering the drug. Interruption in the administration of the drug were similar: 30% with succimer and 27% with placebo. Among families with interruptions, 39% of the children who were given succimer and 45% of the children who were given placebo resumed taking TLC medication.[12] Study participants, those who were administering drug, and physicians and nurses who were monitoring the health of TLC patients were blinded to group assignment.

Before treatment began, we administered the Bayley Scales of Infant Development-II.[16] At 36 months of follow-up, we adminis-

tered the Wechsler Preschool and Primary Scales of Intelligence-Revised[17] and the Developmental Neuropsychological Assessment (NEPSY),[18] a battery of tests designed to identify neuropsychological deficits that can interfere with learning. We also administered the Conners' Parent Rating Scale–Revised[19] to the primary caregiver. The Conners' Parent Rating Scale–Revised yields scales that provide 3 scores that are applicable to younger children: oppositional behavior, hyperactivity, and an attention-deficit/hyperactivity disorder index. These instruments were administered in 2 clinic visits to avoid undue fatigue. Assessment of caregiver intelligence occurred during another visit with the short form of the Wechsler Adult Intelligence Scale–Revised.[20] TLC psychometricians were unaware of subjects' blood lead levels or treatment arm assignment. Results of all of these evaluations have been reported previously.[13,14]

As the children reached school age, we elected to test them at age 7 years and again at 7 years, 6 months rather than assessing them at 5 years since randomization. This decreased the variability introduced by testing children at different ages and should not have introduced variability as a result of the time since treatment, because by age 7 the blood lead concentrations had been the same in the children who were given succimer or placebo for 3 years or more.

We wanted to evaluate the children's cognitive, behavioral, psychological, and school performance broadly but without exceeding their attention spans or making the testing so inconvenient as to compromise follow-up. We also wanted to remain within hypothesis-driven inference. We thus selected and administered an array of standardized neuropsychological instruments and tested hypotheses about specific functional domains by choosing applicable subtests from our battery of measures. The global domains and standardized instruments used to evaluate them and selected subscales are presented in Table 1. The domains were chosen a priori on the basis of previous evidence showing an effect of lead exposure or on mechanistic grounds.[21] Although a behavioral "signature" for lead has not been identified conclusively, deficits in the areas outlined in Table 1 have been related to early exposure to lead in a large number of epidemiologic studies.[22] In selecting the core outcome variables, we examined the pattern of covariance among the TLC neuropsychological measures and used these data to minimize the correlation among the selected primary outcomes. Treatment group–specific results were not available until after we had selected the primary dependent neuropsychological variables examined in this report.

The measures listed in Table 1 yield a large number of variables representing different aspects of performance within a given domain. We decided to examine specific subscales that best reflect TLC hypotheses regarding the effect of lead on child development and the expectation that treatment with succimer would result in better performance. Full-Scale IQ was selected as an index of overall intellectual attainment, and the NEPSY Attention/Executive Functions core domain standard score and Conners Continuous Performance Test d-Prime (perceptual sensitivity or the ability to discriminate targets from nontargets) T score were selected to represent executive functions and attention. The California Verbal Learning Test for Children List A Learning and Learning Slope index T scores were selected to reflect verbal learning and memory, and the Broad Reading standard score from the Woodcock Language Proficiency Battery-Revised was selected to index overall reading ability, including basic reading skills and comprehension. The Externalizing Problems subscale T score from the Behavioral Assessment System for Children parent rating scale was selected to reflect aggressiveness, hyperactivity, and conduct problems in the home, and the Adaptive Skills and School Problems T scores from the teacher form of the scales were selected to index adaptability, social skills, leadership, study skills, and attentional and learning problems in the classroom. Performance times for the right- and left-handed rapid sequential movements tasks from the Neurologic Examination for Subtle Signs were converted to $z$ scores using the SDs obtained from normative data for 7-year-old right- and left- handed boys and girls. These $z$ scores were averaged across tasks to obtain a composite index of neuromotor speed. Hit reaction time from the Conners' Continuous Performance Test was examined as another measure of neuromotor speed.

### Statistical Methods

We used the 2-sample $t$ test to compare unadjusted mean scores between the 2 treatment groups. We also used multiple linear regression analysis to adjust the mean group differences for a set of baseline covariates chosen in advance. These covariates included clinical center, baseline blood lead level, use of Spanish in the home, race, gender, baseline age, caregiver's IQ, and child's baseline score on the Bayley Scales of Infant Development-II Mental Development Index. All analyses were "intent to treat." Because drug therapy was complete long before the results of follow-up testing, there was no need for stopping rules or interim analyses.

## RESULTS

The trial participant flow is shown in Fig 1. We initially assessed 1854 subjects for eligibility. Of these, 1074 were excluded for not meeting eligibility criteria ($N = 922$), and 152 families refused to participate. The vast majority of ineligible referrals had repeat blood lead levels <20 $\mu$g/dL. A total of 780 subjects were randomized, with 396 children allocated to active drug and 384 allocated to placebo. Of these, 43 and 68 families discontinued treatment in the placebo and succimer groups, respectively. Discontinuation of treatment could occur in 2 ways. First, the study pediatrician could decide to stop drug because of suspected side effects or because of an increase in blood lead concentration above 44 $\mu$g/dL, requiring chelation therapy outside the TLC regimen. Second, the family could refuse to accept an additional round of treatment, either actively or passively (by missing treatment appointments). Children who discontinued treatment and participated in the study through 7 years are included in the intent-

**TABLE 1.** TLC Neuropsychological Domains and Instruments

| Neuropsychological Domains | Instrument (Scale) |
|---|---|
| Cognition, Learning, and Memory | |
| Intellectual Attainment | Wechsler Intelligence Scale for Children-III[23] (Full-Scale IQ) |
| Attention/Executive Functions | NEPSY-A Developmental Neuropsychological Assessment[18] (Attention/Executive Functions subscale) |
| | Conners' Continuous Performance Test[24] (d Prime) |
| Verbal Learning and Memory | California Verbal Learning Test for Children[25] (List A Memory and Learning Slope) |
| Reading | Woodcock Language Proficiency Battery–Revised[26] (Broad Reading Score) |
| Behavior | |
| Behavioral Conduct | Behavioral Assessment System for Children–Parent Rating Scale[27] (Externalizing Problems) |
| Behavioral and Academic Conduct | Behavioral Assessment System for Children–Teacher Rating Scale[27] (Adaptive Skills, Externalizing Problems, School Problems) |
| Neuromotor | |
| Neurological | Neurological Examination for Subtle Signs[28] (Rapid Sequential Movements Time) |
| Motor Speed | Conners' Continous Performance Test[24] (Hit Reaction Time) |

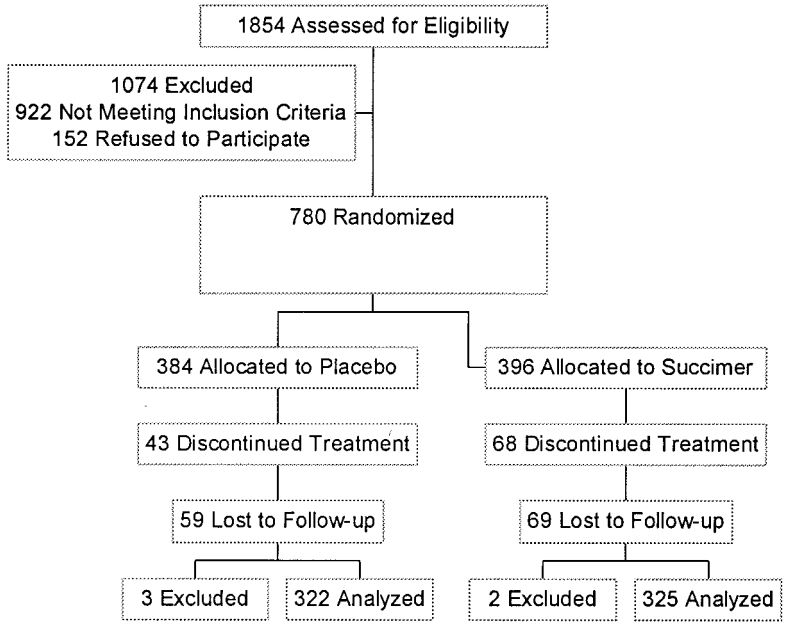


**Fig 1.** Flow of patients through the TLC clinical trial. Children who discontinued treatment and participated in the study through 7 years were included in the intent-to-treat analyses.

to-treat analyses. Succimer and placebo groups that discontinued treatment did not differ with respect to mean blood lead level at baseline (27.4 and 27.6 $\mu$g/dL respectively) or mean blood lead concentration at 7 years of age (8.0 and 8.3 $\mu$g/dL respectively). Furthermore, there were no significant differences between the placebo and succimer patients who discontinued treatment with respect to 25 potential adverse physiologic or behavioral consequences or reactions except for a higher prevalence of elevated Alanine aminotransferase in children on active drug ($N = 8$) when compared with placebo control subjects ($N = 0$; $P \leq .05$). In the present wave, a total of 128 subjects were lost to follow-up: 59 in the placebo group and 69 in the active drug arm. Three subjects in the placebo group and 2 subjects in the succimer group were excluded from the final analysis because of conditions affecting mental or neuromotor status that are unlikely to be related to their exposure to lead (autism spectrum disorder, epilepsy, retinal degeneration).

The 2 treatment groups were balanced with respect to baseline characteristics (Table 2). Thus, the unadjusted and adjusted estimates of treatment effects will be similar. The largest observed difference in blood lead level, 11 $\mu$g/dL (0.5 $\mu$mol/L), occurred 1 week after the beginning of treatment (Fig 2). The mean blood lead concentration of the succimer-treated children was 4.5 $\mu$g/dL (95% confidence interval [CI]: 3.7–5.3 $\mu$g/dL [0.22; 0.18–0.26 $\mu$mol/L]) lower than that of placebo children over the 6-month period after initiation of treatment, and 2.7 $\mu$g/dL (95% CI: 1.9–3.5 $\mu$g/dL [0.13; 0.09–0.17 $\mu$mol/L]) lower over the 12-month period after initiation of treatment.[11] At 7 years of age, the average blood lead concentration of succimer-treated children was 8.0 $\mu$g/dL (SD: 4.0 $\mu$g/dL [0.38 $\mu$mol/L; 0.19 $\mu$mol/L]), whereas the average for children in the placebo arm was 8.0 $\mu$g/dL (SD: 4.1 $\mu$g/dL [0.38 $\mu$mol/L; 0.20 $\mu$mol/L]). The percentage of children with blood lead concentration >10 $\mu$g/dL (0.48 $\mu$mol/L) at 7 years was 25% in the succimer group and 27% in the placebo arm. Only 1% of children in the succimer and placebo groups had 7-year blood lead concentration in excess of 20 $\mu$g/dL (0.96 $\mu$mol/L).

Five of the children who were given succimer and none of those who were given placebo were hospitalized for trauma, with no common pathway or site. In addition, trauma was noted in the history or physical examination in 15% of the children who were given succimer and 10% of those who were given placebo. There was no other category or individual symptom or laboratory abnormality at significant excess in either group.[12] Full tables are provided on the study web site (dir.niehs.nih.gov/direb/tlc1/home.htm). We monitored the children's growth and found that the subjects who were given succimer had grown 0.27 cm (95% CI: 0.11–0.42) less in the first 9 months of follow-up and 0.43 cm (95% CI: 0.09–0.77) less over 34 months of follow-up.[29] At the final follow-up assessment at ~7 years of age, the height of succimer-treated children was shorter by an average of 1.17 cm (95% CI: 0.41–1.93) after adjusting for age, gender, ethnicity, clinical center, and gender-specific $z$ scores for height at baseline.[30]

Table 3 presents the unadjusted mean scores obtained for TLC neuropsychological outcomes by treatment arm. No statistically significant differences were observed between succimer- and placebo-treated children in the areas of cognition, behavior, learning, memory, attention, and neuromotor performance. In unadjusted comparisons, scores favored the succimer group in 6 of 12 outcomes.

Figure 3 presents the adjusted normalized effect of succimer on cognitive, behavioral, learning, memory, and neuromotor scores. The standardization was achieved by dividing the estimated values and 95% CIs for the covariate-adjusted difference between the means in the succimer and placebo groups by the SD of the particular outcome variable. We defined the

**TABLE 2.** Baseline Characteristics of Enrolled Children Followed to Seven Years of Age According to Treatment Group

| Characteristic | Placebo Group ($N$ = 322; Mean [SD]) | Succimer Group ($N$ = 325; Mean [SD]) |
|---|---|---|
| Age, mo | 25 (5) | 25 (6) |
| Blood lead level, $\mu$g/dL | 26 (5) | 27 (5) |
| Weight, kg | 12.4 (1.9) | 12.3 (2.0) |
| Body surface area (m$^2$) | 0.50 (0.1) | 0.50 (0.1) |
| Reported birth weight† | 3171 (624) | 3140 (552) |
| Bayley Scales of Infant Development | | |
| Mental Development Index‡ | 82 (13) | 84 (13) |
| Psychomotor Development Index§ | 92 (13) | 93 (14) |
| Caregiver's IQ‖ | 79 (11) | 81 (11) |
| Female | 44% | 47% |
| Ethnicity | | |
| Hispanic | 8% | 6% |
| Black | 75% | 79% |
| Single parent | 71% | 71% |
| Parent with less than a high school education | 40% | 39% |
| At least 1 employed parent | 44% | 40% |
| Annual family income | | |
| <$10 000 | 38% | 38% |
| ≥$10 000 | 26% | 28% |
| Unknown | 37% | 35% |
| Parent on public assistance | 96% | 95% |

* Convert to $\mu$mol/L ([$\mu$g/dL] × 0.04826).
† These data were available for 302 children in the placebo group and 311 children in the succimer group.
‡ These data were available for 313 children in the placebo group and 320 children in the succimer group.
§ These data were available for 275 children in the placebo group and 283 children in the succimer group.
‖ These data were available for 318 children in the placebo group and 315 children in the succimer group.

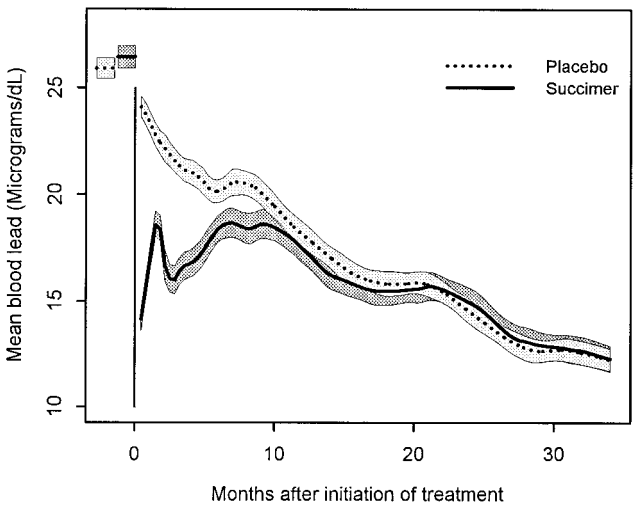


**Fig 2.** Mean blood lead levels and 95% pointwise CIs (shaded areas) at baseline and after the initiation of treatment in children in the succimer and placebo groups. Rectangles in the upper left represent the baseline values, which were measured ~9 days before treatment was initiated. Means for the curves were calculated by locally weighted regression.

effect of succimer as the covariate-adjusted difference between the mean score in the succimer group and mean score in the placebo group for outcomes for which a higher value is optimal. For outcomes for which higher values are less desirable, we defined the effect of succimer as the covariate-adjusted difference between the mean score in the placebo group and the mean score in the succimer group. The reversal of the sign of the difference unifies interpretation of the effect of treatment as all positive signs favor active drug intervention.

The adjusted effect of treatment for the Attention and Executive Functions core domain score from the NEPSY reached statistical significance ($P$ = .045), favoring the placebo group. All other effects of treatment were nonsignificant. In adjusted analyses, results favored the succimer group in 4 of 12 outcomes.

We previously reported a significant relationship between baseline and concurrent blood lead levels and IQ assessed at the last follow-up at 3 years after randomization.[14] Although we observed no significant effects of treatment at that time or in the present analysis, blood lead levels at 7 years were also significantly associated with poorer scores on a number of TLC neuropsychological outcomes after covariate adjustment. Concurrent blood lead levels were associated with poorer scores for Full-Scale IQ ($\beta$ = −0.42, standard error [SE] = 0.12, $P$ < .001) and Reading ($\beta$ = −0.50, SE = 0.18, $P$ < .01) and an increase in teacher-reported Externalizing Problems ($\beta$ = 0.47, SE = 0.14, $P$ < .01), parent-reported Externalizing Problems ($\beta$ = 0.67, SE = 0.16, $P$ < .001), and teacher-reported School Problems ($\beta$ = 0.51, SE = 0.13, $P$ < .001).

## DISCUSSION

The psychometric and behavioral assessments of lead-exposed children who were randomized to out-

**TABLE 3.** Unadjusted Mean TLC Neuropsychological Outcome Scores by Treatment Arm*

| Variable | Succimer Group | | | Placebo Group | | | Succimer-Placebo | | |
|---|---|---|---|---|---|---|---|---|---|
| | *N* | Mean | SD | *N* | Mean | SD | *P* Value | Difference | 95% CI |
| Cognition (WISC-III, NEPSY, WLPB-R) | | | | | | | | | |
| Full-Scale IQ | 323 | 86.9 | 13.2 | 321 | 86.5 | 13.4 | 0.67 | 0.4 | (−1.6 to 2.5) |
| Attention/Executive Functions | 300 | 86.3 | 16.5 | 293 | 88.1 | 17.6 | 0.20 | −1.8 | (−4.5 to 1.0) |
| Reading | 302 | 94.8 | 18.4 | 298 | 93.9 | 18.5 | 0.53 | 1.0 | (−2.0 to 3.9) |
| Behavior (BASC)* | | | | | | | | | |
| Adaptive Skills (Teacher) | 259 | 46.6 | 9.7 | 272 | 46.0 | 9.2 | 0.45 | 0.6 | (−1.0 to 2.2) |
| Externalizing Problems (Teacher) | 266 | 55.2 | 13.9 | 274 | 55.3 | 12.1 | 0.93 | −0.1 | (−2.3 to 2.1) |
| School Problems (Teacher) | 267 | 55.9 | 12.4 | 275 | 56.5 | 12.1 | 0.56 | −0.6 | (−2.7 to 1.5) |
| Externalizing Problems (Parent) | 325 | 58.8 | 16.5 | 323 | 57.2 | 14.1 | 0.18 | 1.6 | (−0.8 to 4.0) |
| Learning and Memory (CVLT-C)* | | | | | | | | | |
| List A Memory | 325 | 43.4 | 11.3 | 320 | 43.9 | 11.8 | 0.57 | −0.5 | (−2.3 to 1.3) |
| List A Learning Slope | 325 | −0.4 | 1.1 | 320 | −0.4 | 1.2 | 0.87 | 0.0 | (−0.2 to 0.2) |
| Attention (CPT)* | | | | | | | | | |
| d Prime | 287 | 55.2 | 9.8 | 285 | 56.3 | 9.9 | 0.16 | −1.2 | (−2.8 to 0.5) |
| Neuromotor (CPT, NESS)* | | | | | | | | | |
| Hit Reaction Time | 287 | 42.7 | 13.1 | 285 | 42.6 | 12.8 | 0.87 | 0.2 | (−2.0 to 2.3) |
| Sequential Movements Time | 286 | 1.0 | 1.3 | 279 | 0.9 | 1.3 | 0.53 | 0.1 | (−0.1 to 0.3) |

WISC-III indicate Wechlser Intelligence Scales for Children-III; WLPB-R, Woodcock Language Proficiency Battery–Revised; BASC, Behavioral Assessment System for Children; CVLTC, California Verbal Learning Test for Children; CPT, Conners' Continuous Performance Test; NESS, Neurological Examination for Soft Signs.

* Higher scores are optimal for the variables Full-Scale IQ, Attention/Executive Functions, Reading, Adaptive Skills, List A Memory, List A Learning Slope, and Hit Reaction Time. Lower scores are optimal for Externalizing Problems, School Problems, d Prime, and Sequential Movements Time.

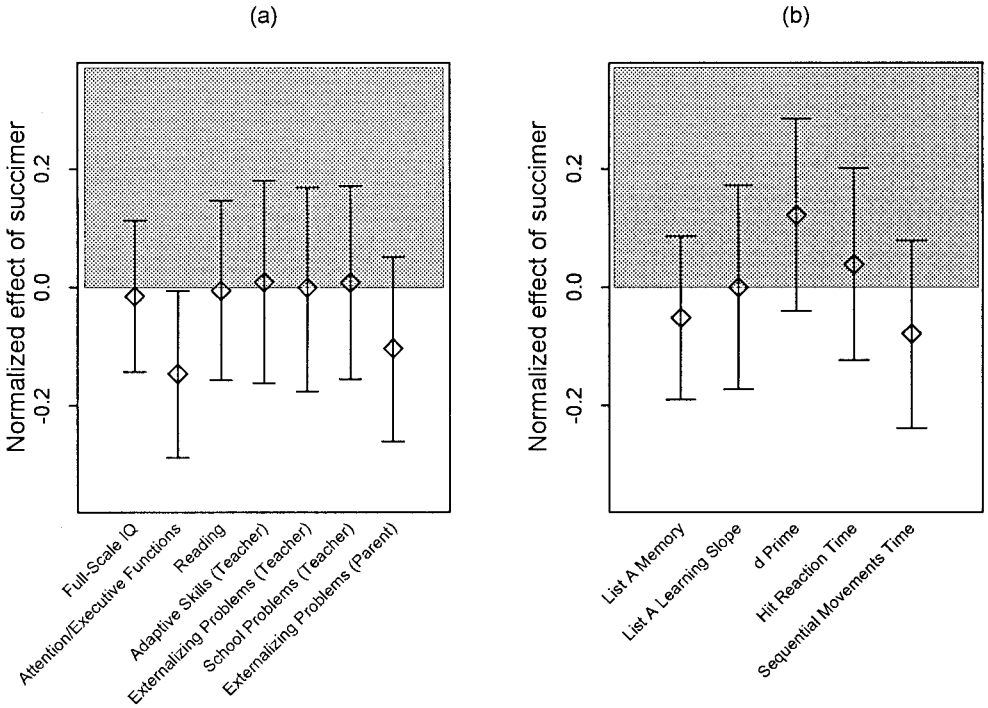


**Fig 3.** Normalized effects of succimer on cognitive, behavioral, learning, memory, attentional, and neuromotor TLC measures. Scores within the shaded areas favor the succimer arm, whereas those below the shaded areas favor the placebo group. The effect of succimer is defined as the succimer-placebo difference for Full-Scale IQ, Attention/Executive Functions, Reading Adaptive Skills (Teacher), List A Memory, List A Learning slope, and Hit Reaction Time, and as the placebo-succimer difference for Externalizing Problems (Parent), Externalizing Problems (Teacher), School problems (Teacher), d Prime, and Sequential Movements Time.

patient chelation or placebo therapy in the TLC study revealed no benefit of therapy at age 7 years. Unlike our first wave of follow-up, for which assessments were conducted over a relatively broad age range (48–70 months), the testing reported here was conducted in a more carefully controlled age window and after children had entered school. Testing at age 7 allows assessment of cognitive and performance skills that are absent or inaccessible in the preschool-aged child. The absence of benefit at this later age adds credence to the earlier negative findings[13] and reiterates the failure of chelation therapy to alter cognitive and behavioral outcomes in preschool children with blood lead levels in the range of 20 to 44 $\mu$g/dL.

In our study, succimer seemed to be a safe drug in

the sense that no important or irreversible side effects could be attributed directly to its administration. Our hypothesis was that children within the succimer group would perform better on our battery of neuropsychological tests when compared with placebo-treated control subjects. Nevertheless, 4 small differences between drug and placebo groups were of slight concern. These included a small but statistically significant deficit in linear growth in drug-treated children as compared with placebo-treated children, a modest but statistically significant excess of hospitalized and outpatient injury events in the first 3 years of follow-up, and small but statistically nonsignificant deficits in the primary cognitive endpoints measured at 3 years of follow-up[13] and 1 statistically significant neuropsychological deficit in succimer-treated children at 7 years (the Attention and Executive Functions core domain score from the NEPSY). Causal mechanisms for any of these findings are unclear, and 1 or more of them may be a matter of chance. We have previously speculated that succimer may enhance lower level neurotoxicity by increasing the transport of lead across the blood-brain barrier.[14] However, the experimental evidence so far demonstrates a reduction in brain lead levels in succimer-treated rodents,[31,32] reductions in liver but not skeletal lead levels in succimer-treated juvenile monkeys,[33] and no change in primate brain lead levels.[34] We further note that succimer has a prominent and unpleasant odor, and it is possible that administration of such a substance to small children 3 times daily over many weeks in early life could have minor negative impacts on feeding behavior or other parent–child interactions. This is consistent with parental reports of externalizing problems in their children, which, although not statistically significant, were more common in the succimer group (Fig 3).

Our failure to demonstrate developmental benefits of succimer therapy could be attributed to a number of factors that we have previously discussed.[13] The difference in blood lead concentration between children who were administered succimer and those who were given placebo exceeded 10 $\mu$g/dL (0.48 $\mu$mol/L) only briefly. The mean blood lead concentration of the succimer-treated children was 2.7 $\mu$g/dL (0.13 $\mu$mol/L) lower than placebo children over the 12-month period after initiation of treatment. Therefore, it could be argued that the failure of our study to demonstrate significant differences on neuropsychological outcomes is attributable to the small differences in achieved blood lead concentrations. Nevertheless, succimer is the most effective chelating agent currently available. Furthermore, our treatment regimen resulted in a higher loading dose than those prescribed in the phase 2 clinical trials of succimer because the child's body surface area rather than weight was used to prescribe TLC patients' dose.[12] Compliance was very good as determined by medication diaries and pill count. We consider it improbable that another chelation regimen would have been more effective. However, our results still must be viewed as specific to the treatment regimen followed by TLC, not all possible regimens.

We acknowledge that TLC follow-up studies extended to an age when children's neurocognitive development is incomplete. Lead not only disrupts established neurocognitive functions but also may affect those functions that are developing at the time, as well as those that have yet to develop. This raises the possibility of late-emerging effects of neurotoxicity. Although executive function skills are not absent in young children, some aspects of executive functioning are difficult to assess in this age group. For example, the neural systems and substrates that play a role in certain complex executive functions involving planning, organization, adaptability, and inhibition are among the last to mature in the brain.[35–37] For this reason, behavioral sequelae of early injury to these neural systems may become fully evident only as a child becomes older and the demands for higher level functioning increase. Although additional follow-up of this cohort has not been planned at this time, the possibility that treatment of TLC children may have long-term neurodevelopmental benefits cannot be ruled out.

In its most recent guidelines for the treatment of lead-exposed children, the CDC has omitted any recommendation for the chelation of children with blood lead levels $<45$ $\mu$g/dL.[38] Succimer is labeled only for children with higher blood lead levels. The findings of this study do not support any changes to current practice. One might ask whether, in the absence of a recommended medical treatment at these levels, high-risk children still should be screened for lead exposure. We strongly believe that they should, principally because such screening can trigger environmental steps that can limit additional exposure. More effective public health policies to assist parents with such environmental interventions are needed badly. The elimination of childhood lead poisoning by the year 2010 remains a worthwhile goal, and progress in this direction can be assessed only if screening continues. Our efforts, however, should go beyond mere screening for cases. Indeed, the first line of defense against this avoidable environmental disease should be the screening of homes with potentially hazardous sources of exposure. By the time a child is identified as lead poisoned, the damage already may have been done with possibly irreversible consequences.[39]

In summary, these new follow-up data of children enrolled in a randomized trial of outpatient chelation therapy confirm that the therapy led to no benefit in the cognitive and behavioral endpoints. Because chelation seems to have no proven developmental benefits in children with blood lead levels between 20 and 45 $\mu$g/dL, it is important to limit additional environmental exposure in these children, as well as in the much larger number of children with lower blood lead levels that may also impart a risk for suboptimal neurodevelopment.[7]

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