ORIGINAL ARTICLES

Androgen Treatment Effects on Motor Function, Cognition, and Behavior in Boys with Klinefelter Syndrome

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Objectives To examine the effects of early low-dose androgen on motor, cognitive, and behavioral function in prepubertal boys with Klinefelter syndrome (47,XXY).

Study design Double-blind trial of 84 boys, ages 4-12 years, randomized to oxandrolone (Ox; 0.06 mg/kg daily; n = 43) or placebo (Pl; n = 41) for 24 months. Standardized assessments were performed at baseline and every 12 months for 24 months evaluating motor, cognitive, and behavioral function.

Results The 24-month outcomes were better in the Ox vs. Pl group on 1 of 5 primary endpoints (motor function/strength): Bruininks Visual-Motor scale ($P = .005$), without significant differences between the 2 groups for the other 4 components. Secondary analyses suggested improvement in the Ox vs. Pl group in the anxiety/depression ($P = .03$) and social problems ($P = .01$) scales on the Child Behavior Checklist, anxiety ($P = .04$) on the Piers Harris Self Concept Scale, and interpersonal problems ($P = .02$) on the Children's Depression Inventory, without significant differences in hyperactive or aggressive behaviors.

Conclusions This double-blind, randomized trial demonstrates that 24 months of childhood low-dose androgen treatment in boys with Klinefelter syndrome benefited 1 of 5 primary endpoints (visual-motor function). Secondary analyses demonstrated positive effects of androgen on aspects of psychosocial function (anxiety, depression, social problems), without significant effects on cognitive function, or hyperactive or aggressive behaviors. *(J Pediatr 2017;185:193-9).*

Trial registration ClinicalTrials.gov: NCT00348946.

Klinefelter syndrome,[1] an underdiagnosed genetic disorder that occurs in 1/500-1000 males,[2] is defined by the chromosome karyotype 47,XXY and has characteristic physical, cognitive, and behavioral phenotypes. The Klinefelter syndrome physical phenotype includes testicular failure (androgen deficiency) and tall stature.[3] The neurocognitive phenotype includes language-based learning difficulties and impairments in motor function, working memory, executive function, and attention.[3-5] Approximately 50%-75% of boys with Klinefelter syndrome demonstrate a specific reading/language disability, and 60%-86% require special education services.[6,7] The behavioral profile includes shyness, diminished self-esteem, increased anxiety, depression, and social problems.[8-10] The potential contribution of early childhood androgen deficiency vs. the second X chromosome to these features is not known.

Clinical evidence of early childhood androgen deficiency in boys with Klinefelter syndrome comes from reports of small testes and genitalia in infancy and childhood,[11-13] as well as eunuchoidal body proportions, hypotonia, and decreased muscle mass.[3] The question of whether or not testosterone is low during infancy and childhood among boys with Klinefelter syndrome is not resolved. Moreover, testosterone levels in blood in Klinefelter syndrome have been reported as low for age, low normal, or normal in childhood and adulthood,[13-17] and 1 study of infants with Klinefelter syndrome reported increased testosterone levels.[18] Evidence of testosterone deficiency in this study's 4- to 12-year-old cohort comes from recently published baseline testosterone levels, which were significantly lower than the mean for age and were below the lower limit of normal in almost one-half of subjects.[19]

Because testosterone affects typical brain development in males, this early androgen deficiency in Klinefelter syndrome is likely to have an impact on motor and cognitive function and on behavior. Muscle mass and strength, motor function, and self-image have been reported to improve with androgen replacement in adolescents and adults with Klinefelter syndrome[5,20,21] and in other populations.[22,23] In this randomized, placebo-controlled study, we aimed

AR	Androgen receptor
BOT	Bruininks-Oseretsky Test of Motor Proficiency
CBCL	Child Behavior Checklist
DAS-II	Differential Ability Scales, 2nd edition
OX	Oxandrolone
Pl	Placebo
SES	Socioeconomic status

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to restore normal childhood levels of androgen for 2 years in prepubertal boys with Klinefelter syndrome through treatment with a synthetic oral androgen (oxandrolone [Ox]). Low-dose androgen supplementation in boys with Klinefelter syndrome has not, to our knowledge, been previously evaluated prospectively. We postulated that low-dose, physiological androgen replacement during childhood would improve the primary outcome, namely, motor function/strength. Secondary analyses evaluated effects on cognition and psychosocial function.

Methods

Participants were recruited from a broad geographic and socioeconomic distribution through the support of the advocacy organization The Association for X and Y Chromosome Variations: AXYS/KS&A, by direct referral, and through the Internet. Inclusion criteria were karyotype diagnosis of Klinefelter syndrome (47,XXY and variants [48,XXXY, 48,XXYY]), <50% mosaicism for 46,XY cell line, age 4-12 years, no evidence of spontaneous onset of puberty (testicular size ≤ 4 mL), and no treatment with androgen in the preceding year. Exclusion criteria for this study were karyotypes including 46,XX males and 47,XYY males, intellectual disability, defined as baseline verbal or nonverbal Differential Ability Scales, 2nd edition (DAS-II) cluster standard scores <70 (<-2 SD), and the inability to complete the cognitive and behavioral evaluation. A total of 9 subjects (3 Ox and 6 Pl) were excluded from these analyses, secondary to intellectual disability.

The study (conducted in 2007-2011) was approved by the Human Subjects Committee of Thomas Jefferson University and was registered with ClinicalTrials.gov (NCT00348946). Written informed consent was obtained from parent(s)/guardian and assent from patients. Participants were assigned randomly to treatment groups in a 1:1 ratio using computer-generated randomization. Study medications were secured and dispensed by the Thomas Jefferson University research pharmacy. Participants and investigators were blinded to treatment group assignment.

The protocol-specified Ox dose was 0.06 mg/kg per day, rounded to the nearest 2.5 mg, and Ox or placebo (Pl), for 24 months. A protocol-specified dose reduction schedule was used, whereby dose was reduced by 50% if low-density lipoprotein cholesterol was > 159 mg/dL, high-density lipoprotein cholesterol was < 20 mg/dL, liver function test (serum glutamic pyruvic transaminase) exceeding twice the upper limit of normal for the assay (>90 IU/L), Tanner 2 pubic hair in boys < 8 years of age, bone age advancement > 12 months/6-month interval and bone age greater than chronologic age, and systolic or diastolic blood pressure > 95th percentile for age and sex. We assessed compliance by having families fill out dosing cards and by counts of dispensed and returned capsules at each visit.

Safety Measures

Safety was evaluated at each visit by history, physical examination, and laboratory analyses, and results have been published.[19] An independent Data and Safety Monitoring Board reviewed annual interim analyses and included experts in statistics, endocrinology and pediatrics.

Table I. Cognitive and behavioral evaluation

Primary outcome analyses
Domain 1: Motor function/strength
BOT
Physical and Neurological Evaluation for Soft Signs (PANESS)
Hand strength dynamometer
Domain 2: Cognitive function and language
Differential Ability Scales, 2nd edition
Domain 3: Working memory/executive function/attention
Digit span backward
Verbal fluencies: (A Developmental Neuropsychological Assessment, NEPSY)
Conners' Continuous Performance Test (CPT-II; 5-18 + y)/Kiddie CPT (4-5 y)
Domain 4: Self-image and social function
Parent questionnaires (filled out by mother in all cases except 2)
CBCL
Child self-report questionnaires (completed by the child)
Self-concept: The Piers-Harris Self Concept Scale (SCS), 2nd edition (ages 7-18 y).
Depression: the Children's Depression Inventory (CDI)

Study Assessments

Subjects were evaluated on outcome measures at baseline and 12 and 24 months. The standardized cognitive and behavioral evaluation was performed by trained psychometricians over 3-4 hours (**Table I**). For more detail, see the **Appendix** (available at www.jpeds.com). Socioeconomic status (SES) was derived from the Hollingshead 2-Factor Index.[24]

Statistical Analyses

Analyses were performed using SAS software (9.2, SAS Institute, Inc, Cary, North Carolina). For baseline comparisons, we used *t* tests for continuous variables and Fisher exact tests for dichotomous variables. For longitudinal changes, we used a mixed model of repeated measures analysis of covariance, with fixed effects of treatment group and the 24-month visit, comparing the change from baseline at 24 months in the Ox and Pl groups and adjusting for baseline differences in values, age, and SES. The 12 month results are part of this mixed model repeated measures analysis, but only *P* values for the 24-month data are presented. Data are presented as mean ± SD or as least squares mean ± SE. Our primary analysis specified five primary outcomes from the motor/strength domain, including the Bruininks-Oseretsky Test of Motor Proficiency (BOT) subscales of (1) visual motor control, (2) upper limb speed, and (3) strength, hand strength dynamometer—dominant hand, and Physical and Neurological Evaluation for Soft Signs finger—dominant hand. For these 5 primary efficacy measures comprising the primary endpoint, *P* values are provided and the alpha level for statistical significance was set at 0.05/5 = 0.01 (2-tailed). Secondary analyses included measures of cognitive and social/behavioral function. There was no prespecified plan for adjustment for multiple comparisons in the analysis of secondary outcomes, and an alpha of ≤0.05 (2-tailed) was considered to be statistically significant. To evaluate the baseline proportion of clinically significant scales

(% impaired), scores were divided into clinically significant (t score ≥ 1.7 SD [≥67]) for the Child Behavior Checklist (CBCL).[25]

Results

Enrollment for this study was from June 20, 2007, until August 31, 2009. A total of 93 boys enrolled (Ox [n = 46] or Pl [n = 47]; **Figure 1**; available at www.jpeds.com), and 84 were deemed eligible for this study.

Karyotypes in the 84 included 81 47,XXY, 2 mosaic 47,XXY/46,XY, and 1 Klinefelter syndrome variant (X;Y translocation). Diagnosis was made prenatally or in infancy in 69%. Participants came from 31 US states and Canada from a broad range of SES and parental education levels. Prior psychiatric diagnoses included attention deficit hyperactivity disorder in 28% and autism spectrum disorder in 11%.

The 2 groups (Ox vs. Pl) had similar baseline IQ and SES values, but the Ox group was significantly younger ($P < .01$; **Table II**). Results were therefore adjusted for age within the ANCOVA model. A total of 84 and 72 subjects completed the baseline and 24-month cognitive evaluations, respectively (**Figure 1**). No subjects withdrew secondary to significant adverse events, and safety data was reported previously.[19]

A total of 17 of 72 subjects (7 Ox, 10 PL) who completed the 24-month trial had received treatment with testosterone at various dosages and durations in infancy or early childhood for durations of <0.7 year. Those with previous exposure to androgen therapy (23.6%) did not differ with respect to physical or gonadal function outcomes.[26]

Baseline Findings

Primary Outcomes (Domain 1). Baseline performance on the BOT was decreased compared with population means (by approximately 0.5-1.0 SD) and did not differ between groups (**Table III**; available at www.jpeds.com). Grip strength measured by hand dynamometer was in the normal range at baseline.

Secondary Outcomes

Cognitive Function and Language (Domain 2). Verbal and nonverbal DAS standard scores were generally in the normative range (±2 SD) for both groups (Ox, Pl) at baseline (**Table III**). However, subjects with verbal or nonverbal DAS cluster scores < 70 [< -2 SD]) were excluded.

Table II. Baseline demographic and IQ information (mean ± SD)

	Klinefelter syndrome-Ox	Klinefelter syndrome-Pl	*P*-value*
N	43	41	
Chronologic age (y)	6.9 ± 2.2	8.3 ± 2.7	.01
SES	52 ± 10	53 ± 9	.55
% Caucasian	72	76	.92
% 47,XXY	95	95	.99
DAS verbal cluster	95 ± 12	95 ± 16	.67
DAS nonverbal cluster	98 ± 14	99 ± 13	.89

*Fisher exact test or t test.

Working Memory/Attention (Domain 3). For the working memory tests (digit span backward and verbal fluencies), baseline performance was on average in the normative range, and the groups did not differ significantly. For the attention test, the Conners Continuous Performance Test, baseline standard scores tended to be impaired (-1.0-1.5 SD), most severely for omissions and perseverations.

Psychosocial and Behavior Domain (Domain 4)

Child Behavior Checklist. At baseline, scores were within 2 SD of the population mean for many of the behavioral domains. However, boys with Klinefelter syndrome had increased baseline t scores score ≥ 1.7 SD (≥ 67) for CBCL behavior problems 33% (28/84), social problems 29% (24/84), attention problems 35% (29/84), and withdrawn scales 25% (21/84).

Child Scales: Affect and Behavior (Domain 4)

Piers-Harris Self Concept Scale, 2nd Edition, and Children's Depression Inventory. Baseline results were within 1-2 SD of the population means.

Treatment Effects

Dose Reductions. A total of 6 Ox vs. 0 Pl patients had dose reductions for high-density lipoprotein cholesterol that was <20 mg/dL; there were 13 Ox vs. 9 Pl dose reductions for bone age advancement. No patients in either group had dose reductions for pubertal development, blood pressure elevation, or change in liver function tests.

Primary Outcome Analysis (Domain 1). This analysis included 5 measures of motor function/strength: BOT visual-motor control, BOT upper limb speed, BOT strength, Physical and Neurological Evaluation for Soft Signs-dominant hand, hand dynamometer-dominant hand; **Table III**). On 1 of the 5 measures, namely, the BOT visual-motor control subtest, which measures how well the child can coordinate small hand movements and visual responses, the Ox group had better scores than the Pl group at 2 years after controlling for baseline differences and age ($P < .005$; **Figure 2**). The other 4 measures of motor function/strength showed no differences in changes at 24 months for the Ox vs. Pl groups. Grip strength measured by hand dynamometer increased at 24 months for the Ox vs. Pl group, without attaining statistical significance ($P = .06$, dominant hand). Adding the fixed variable of prior testosterone treatment to the ANCOVA model was not significant for any of the primary endpoints in this study except strength in the dominant hand for hand dynamometer in the Ox group (fixed effect for prior testosterone treatment, $P = .02$; ANCOVA model for 2 year change, $P = .047$; 2-year standard score means ± SD for no prior treatment vs prior treatment: Ox: 124 ± 14 vs. 130 ± 14 m, Pl: 118 ± 13 vs 112 ± 18).

Secondary Outcomes Analyses

Cognitive Function and Language (Domain 2). Verbal and nonverbal DAS standard scores did not differ at 24 months between the groups (**Table III**).

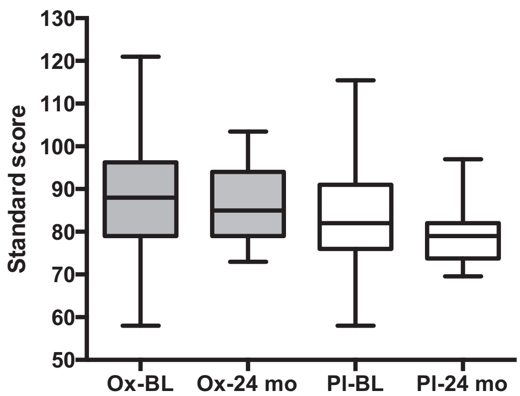

Figure 2. Effects of Ox treatment on BOT visual motor control. Box and whiskers plot of longitudinal baseline and 24 month scores for Ox (*left*) and Pl (*right*). The *solid line* in the box is the median, the box range is the 25th-75th percentile, and the whiskers go up to the largest and go down to the smallest value.

Working Memory/Attention (Domain 3). For the working memory tests (digit span backward and verbal fluencies) and for the attention test (Conners Continuous Performance Test, the groups did not differ significantly over the 24 months study duration; **Table III**).

Psychosocial and Behavior Domain (Domain 4)

Child Behavior Checklist. At 24 months, the Ox group showed significant improvement in the CBCL anxious/depressed ($P < .03$) and social problems scales (acts young, teased, not liked; $P < .01$; **Table III**). Other CBCL subscales including Aggressive, delinquent, or sex problems scales did not differ at 24 months between the treatment groups.

Child Scales: Affect and Behavior

The Piers-Harris Self Concept Scale, 2nd Edition. For the anxiety scale, the Ox group had significantly improved standard scores (better self-esteem; $P < .04$, ANCOVA) at 2 years, compared with the Pl group. Other Piers-Harris subscales did not differ at 24 months between the treatment groups.

Children's Depression Inventory. The Ox group had significantly better outcomes at 24 months on the Children's Depression Inventory interpersonal problems (not getting along with others; $P = .02$, ANCOVA), without significant differences in the other scales.

Discussion

In this randomized, double-blind, placebo-controlled clinical trial, we evaluated 84 boys with Klinefelter syndrome, ages 4-12 years, who were treated with Ox or Pl for 2 years. Important findings at baseline include low performance on the BOT standardized test for motor skills and the Conners Continuous Performance Test for attention. Ox treatment for 24 months resulted in improved visual-motor performance, but did not demonstrate significant effects of androgen treatment on the other 4 co-primary motor function/strength endpoints. There were positive effects of Ox treatment on several aspects of anxiety/depression and social functioning, without adverse effects on behavior. Ox treatment did not have significant effects on most aspects of cognition (general cognition, verbal skills, working memory).

Although testosterone deficiency in boys with Klinefelter syndrome remains an area of debate, support for androgen deficiency occurring earlier in childhood in boys with Klinefelter syndrome includes the frequent lack of the typical neonatal testosterone surge, and the low/low-normal testosterone levels in childhood.[13,27,28] These lower testosterone concentrations are correlated with subsequent diminished testicular and penile growth,[29] altered cortical maturation, and increased social behavior concerns.[30] Prepubertal testosterone levels are often below the detection limit for most assays, and radioimmunoassays (most common method of measuring testosterone) overestimate testosterone levels in children.[31] Thus, whether testosterone levels are low and whether hypogonadism is present in boys with Klinefelter syndrome is not yet resolved.[15] Testosterone replacement in infants, children, and adolescents with Klinefelter syndrome is quite variable with a lack of evidence-based recommendations or generally accepted clinical practice guidelines.[32,33]

The androgen receptor (AR) knockout mouse model supports the notion that testosterone acts physiologically at low levels in childhood because adult male-typical behaviors require AR-mediated androgen signaling early in life.[34] Androgen deficiency and selective impaired learning have also been reported in an XXY mouse model, and testosterone replacement improved psychosocial deficits.[35] Testosterone has organizational effects on the brain, both in utero and throughout life. Exposure to specific sex steroids leads to sex differences in brain and behavior,[36-38] brain volume and cortical thickness, and gray matter and white matter development[39] in animal and human models.[40]

Motor dysfunction and impaired visual-motor integration are cardinal features of Klinefelter syndrome, as reflected in our baseline findings and described by other investigators.[5] In this study, we observed a significant positive effect of Ox on a measure of visual-motor control, but did not observe a significant impact of Ox treatment on other aspects of motor function or strength. Visual-motor integration is required in many activities of daily living and school performance, and this domain has been reported previously to be impaired in Klinefelter syndrome.[5] It is important to note that visual-motor control worsened throughout the 2-year study period in boys treated with Pl, whereas Ox seemed to protect against this decline. Possible mechanisms related to the decline include more severe androgen deficiency and/or increasingly impaired executive function as boys with Klinefelter syndrome grow older.

There have been retrospective reports about the impact of testosterone replacement on cognitive and behavioral outcomes in Klinefelter syndrome. Nonrandomized testosterone replacement in infancy was associated with higher scores in intellectual, language, and neuromotor skills measured at 3 and 6 years of age,[41] and testosterone supplementation in hypogonadal adolescents and adults was associated with improved verbal fluency.[42,43] We did not find differences in cognition or working memory with our selected measurement tools after 24 months of Ox treatment.

Multiple studies have demonstrated an increased risk of attention deficit hyperactivity disorder (inattentive type) in boys with Klinefelter syndrome, with 34%-36% meeting the *Diagnostic and Statistical Manual of Mental Disorders IV* criteria for attention deficit hyperactivity disorder.[44] In this study, Ox treatment for 2 years was not associated with positive or negative effects on attention.

In contrast with the limited effects of Ox on motor or cognitive function of boys with Klinefelter syndrome, we found modest positive effects of Ox on psychosocial functioning as reported by both parent and child. Retrospective studies of early testosterone treatment have been reported to be associated with fewer behavior problems and better social skills later in childhood.[45-47] In the current study, parents of children in the Ox group reported improved CBCL social problems scores (acts young, teased, not liked), and the children themselves reported improvements in interpersonal problems (Children's Depression Inventory) and with less anxiety (Piers Harris). Importantly, both the parents and participants were blinded to their treatment status; therefore, taken together, our study results support modest positive effects of androgen therapy on anxiety and social functioning.

The "standard of medical care" for initiating testosterone replacement therapy in boys with Klinefelter syndrome has typically been after failure of initiation or sustained development of puberty. There are few options for lower dose androgen dosing in childhood. Typically, adult androgen replacement is given using intramuscular injections or alternative formulations available only in higher doses. We chose to use a low-dose, orally administered synthetic androgen treatment, Ox, which is approved by the US Food and Drug Administration, and has been used safely in boys with delayed puberty for >30 years.[48] Ox acts at the level of the AR, is an AR agonist in vivo, and affects androgen-responsive target tissues,[49] but is less virilizing, less hepatotoxic, and less active at a cellular level, compared with testosterone.[50] However, there are several limitations related to Ox. First, clinical assays to quantify serum levels are not available, so the dose could not be titrated within a range. Second, because Ox is a nonaromatizable androgen,[51] it may be less physiological than testosterone, and the aromatization of testosterone to estradiol may have separate, specific effects on brain and behavior. Thus, Ox may offer adjuvant rather than replacement therapy for some physiological and psychosocial symptoms in Klinefelter syndrome.

In this study, dose reductions occurred owing to our predetermined "hard stops." However, the use of a more potent or higher dose androgen, aromatizable or not, may have favorably (or unfavorably) altered the outcomes. Finally, there are likely to be organizational effects of prenatal or early postnatal sex steroids, which may be a "window of opportunity" that cannot be reclaimed with either an aromatizable or nonaromatizable androgen outside of that critical time.

Although this is a large, randomized, controlled trial, it may have been underpowered to detect clinically meaningful benefits of Ox treatment. This lack of power may be especially true for assessments with reduced sample size based on a minimum age (e.g., child questionnaires excluding children <6 years old [33% at start]). The target enrollment was initially set at 150 subjects and the actual enrollment was 93 subjects. This reduced the power to detect statistically significant differences. However, our original power analysis was based on our previous research and the work of others, and it showed that we had >90% power ($\alpha = 0.05$, 2-tailed) to detect significant androgen effects on working memory/executive function for the treatment group vs. the placebo group, with $n = 20$ in each group.

In addition, there may have been study bias based on how the Klinefelter syndrome was diagnosed in our study cohort. Early diagnosis of Klinefelter syndrome in childhood is difficult and the rate of diagnosis is extremely low in childhood; only 10% of cases are identified before puberty with a subsequent rate of ascertainment during lifetime of 25%.[52] The low rate of timely diagnosis is likely due to the fact that many of the classical signs and symptoms of androgen deficiency become evident in adolescence. To achieve the goal of increased early diagnosis in Klinefelter syndrome, it is necessary to increase medical awareness of the disease and in particular to augment pediatricians' knowledge that pathognomonic clinical features of Klinefelter syndrome are often lacking in childhood, but a characteristic cognitive and behavioral pattern is commonly present.[53]

In conclusion, 2 years of treatment with childhood low-dose Ox was associated with positive effects on visual-motor integration and psychosocial function, without affecting most other motor or cognitive outcomes. The convergence between the child and parent measures in domains of social function indicates the results were clinically significant and meaningful. Importantly, there was no increase in negative behaviors with Ox treatment. Dosage individualization based on protocol-defined criteria was a unique aspect of the present study.

These findings need to be further validated with longer term studies. Early diagnosis, together with parental education, developmental interventions, and potentially earlier androgen replacement may contribute to improved outcomes in Klinefelter syndrome, particularly in reduction of the social- psychosocial challenges.[32] Future studies linking hormonal and genetic mechanisms will increase our understanding of the pathogenesis of Klinefelter syndrome and will permit more targeted interventions. ■

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Appendix

Description of Cognitive and Behavioral Tests

1. Assessments of motor function/strength
   A. The Bruininks-Oseretsky Test of Motor Proficiency (BOT)
   B. Physical and Neurological Evaluation for Soft Signs (PANESS)
   C. Hand strength dynamometer
2. **Assessment of general cognition**
   A. Differential Ability Scales, 2nd edition (DAS-II)

Assessment of Working Memory/Attention

A. Digit span backward
B. Verbal fluencies: A Developmental Neuropsychological Assessment (NEPSY)
C. Conners' Continuous Performance Test (CPT-II; 5-18 + y)/Kiddie CPT (4-5 y)

Domain 4. Self-Image and Social Function
Parent Questionnaires

A. The Child Behavior Checklist (CBCL)

Child Self-Report Questionnaires (Completed by the Child).

A. Self-Concept. The Piers-Harris Self Concept Scale (SCS), 2nd edition (ages 7-18 years).
B. Depression. The Children's Depression Inventory (CDI).

Socioeconomic Status (SES): SES was derived from the Hollingshead 2-Factor Index.[20]

Battery of Tests. Assessments of motor function, cognitive function, and working memory.

Scores are expressed as standard scores with mean of 100 and SD of 15, unless indicated otherwise. Higher scores imply better function.

Domain 1. Motor Function/Strength. The tasks used to assess fine and gross motor skills included the 5 primary endpoints: PANESS finger, BOT visual-motor control, BOT upper limb speed, BOT strength, and hand dynamometer-dominant hand.

A. BOT.[1] This battery assesses the child's motor development and includes standard scores (mean = 100, SD = 15) and subtest scores and is normed for sex and age (4-14.5 years). Time: 60 minutes.

B. PANESS (Physical and Neurological Evaluation for Soft Signs)[2] assesses the time required to press thumb to 4 fingers 20 times for the dominant and nondominant hands, with age-specific norms (4-18 years). Time: 5 minutes.

C. Hand strength dynamometer assesses hand strength in the dominant and nondominant hands and includes standard (mean = 100, SD = 15) scores. Dominance was defined as performing 5 of 8 or more tasks with that hand. Normative data are available from subjects ages 5-14 years, according to sex.[3] Time: 10 minutes.

Domain 2. General Cognition and Language. Differential Ability Scales, 2nd edition (DAS-II)[4] provides an age- and sex-standardized assessment of intellectual functioning (General Conceptual Ability; similar to IQ) in children ages 2-17 years of age (mean = 100, SD = 15). The preschool form (ages 4-5 years) is divided into a verbal cluster (including 2 subtests) and a nonverbal cluster (including 2 spatial and 1 nonverbal reasoning subtests). The school age form (ages 6-17) includes 3 clusters. The verbal cluster measures the child's ability to define words and to perform verbal reasoning tasks. The nonverbal reasoning cluster measures the child's inductive and sequential reasoning abilities. The spatial cluster measures visuospatial construction ability, spatial memory, and spatial reasoning. The nonverbal and spatial clusters are computed for children > 6 years of age. Time: 75 minutes.

Domain 3. Working Memory/Attention. A. Digit Span Backward.[5] This task is normed for children ages 5-16 years. Time: 10 minutes.

B. Verbal Fluencies: (A Developmental Neuropsychological Assessment, NEPSY verbal fluency subtest)[6]: semantic fluency measures the number of words the child can name in the categories food and drink (ages 4-12), and phonemic fluency measures the number of words the child can name beginning with the letters F and S (ages 6-12). Time: 10 minutes.

C. Conners' Continuous Performance Test (CPT-II)[7] (5-18 + y)/Kiddie CPT (4-5 y) measures the ability to maintain attention over an extended period of time with a computer task that flashes different letters or pictures repeatedly on the screen and requires child to press the space bar each time a specific letter or picture appeared. Time: 15 minutes.

Domain 4. Self-Image and Social Function
Parent Questionnaires (Completed by the Accompanying Parent). Scores are expressed as *t* scores with mean of 50 and SD of 10, unless indicated otherwise. Lower scores imply better function and higher scores indicate more problem behaviors.

A. The Child Behavior Checklist (CBCL)[8] is a standardized measure of behavior problems and social competency normed for children ages 4-16 and was completed by 1 parent or guardian. The CBCL includes *t* scores for 10 problem behavior areas and for 3 social competency areas (activities, social, and school). Higher scores indicate more problems, with the cutoff for the clinical range at a *t* score of ≥67.[8] The behavior problems scales include internalizing, externalizing, and total behavior domain scores. The 3 social competency scales are scored such that higher scores indicate better social competence. Reliability and validity for the CBCL is well-established and the measure is widely used in child behavior studies.

Child Self-Report Questionnaires (Completed by the Child). A. Self-Concept. The Piers-Harris Self Concept Scale (SCS), 2nd Edition[9] (ages 7-18 years) is a self-report measure of self-concept. Scoring provides a total standard score and scores on

6 subscales: physical appearance and attributes, freedom from anxiety, intellectual and school status, behavioral adjustment, happiness and satisfaction, and popularity.

B. Depression. The Children's Depression Inventory (CDI)[10] is a widely used self-report measure for assessment of depression in children. Reliability, internal consistency and validity have been well-established. The CDI assesses cognitive, affective and behavioral signs of depression in children ages 6-17. Total CDI score reflects the presence of overall depressive symptoms. Additional measures include negative mood (symptoms of sadness, guilt, crying), interpersonal problems (symptoms related to not getting along with others, misbehaving), ineffectiveness (symptoms focusing on difficulties with schoolwork, feelings of inferiority), anhedonia (symptoms of feeling decreased pleasure and fun, sleep or appetite changes, feeling alone, worrying), and negative self-esteem (symptoms of self-dislike, feeling unloved, feeling unsure of the future).

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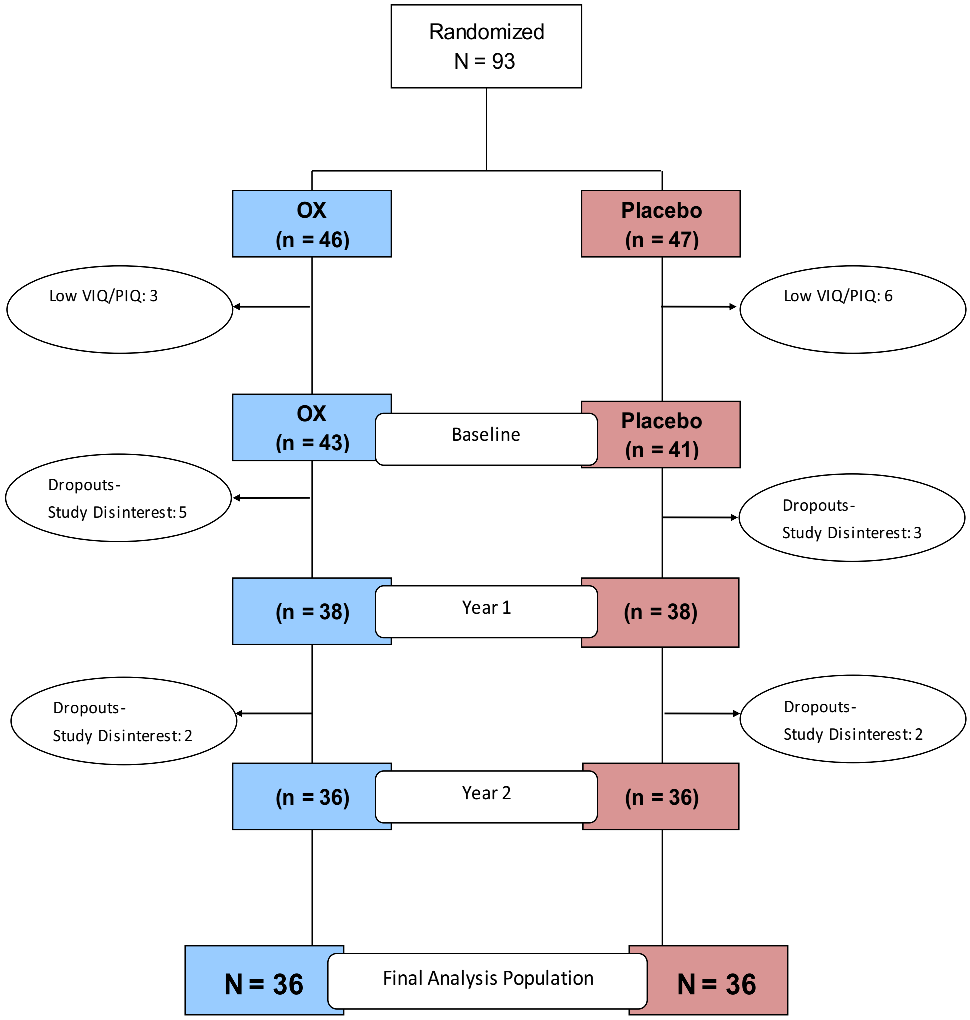

Figure 1. Study disposition. A total of 93 boys were enrolled and randomized (Ox [n = 46] or Pl [n = 47]), and 84 met study criteria. Participant demographics were 75% Caucasian, 1% African American, 9% Hispanic, 5% Asian American, and 10% other. There were 12 dropouts (7 Ox, 5 Pl; 14% dropout rate). Reasons for study discontinuation included lack of interest in all 12. None withdrew because of adverse events or safety reasons. *VIQ/PIQ*, Verbal IQ/performance IQ.

Table III. Longitudinal primary and secondary outcome analysis results (*t* scores, standard scores, mean ± SEM)

Primary outcome analyses	Klinefelter syndrome-Ox BL†	Klinefelter syndrome-Ox 12 mo	Klinefelter syndrome-Ox 24 mo	Klinefelter syndrome-Pl BL	Klinefelter syndrome-Pl 12 mo	Klinefelter syndrome-Pl 24 mo	*P*-value* 24 mo
Domain 1: motor function/strength							
BOT (n) SS§	35	35	35	36	36	36	
BOT upper limb speed	86 ± 2	90 ± 2	92 ± 1	87 ± 2	88 ± 2	89 ± 2	.17
BOT strength	91 ± 2	89 ± 2	88 ± 1	87 ± 2	86 ± 2	85 ± 1	.17
BOT visual-motor control	89 ± 3	85 ± 1	86 ± 1	86 ± 3	84 ± 1	81 ± 1	.005
Hand dynamometer (n) SS	34	34	34	36	36	36	
Mean SS§ dominant hand	116 ± 2	119 ± 2	123 ± 2	114 ± 3	118 ± 2	118 ± 2	.06
PANESS	21	21	21	24	24	24	
PANESS dominant hand	80 ± 5	82 ± 4	91 ± 3	83 ± 5	82 ± 4	91 ± 3	.87
Domain 2: cognitive function, verbal							
DAS SS§ (n)	35	35	35	36	36	36	
General conceptual ability	95 ± 2	96 ± 2	96 ± 2	95 ± 2	94 ± 2	94 ± 2	.44
Verbal cluster	94 ± 2	95 ± 2	92 ± 2	97 ± 3	93 ± 2	90 ± 2	.57
Nonverbal cluster	98 ± 2	101 ± 2	102 ± 2	99 ± 2	98 ± 2	101 ± 2	.55
Spatial cluster (n)	94 ± 3 (22)	97 ± 2 (22)	96 ± 2 (22)	90 ± 3 (24)	93 ± 2 (24)	94 ± 2 (24)	.65
Domain 3: working memory/executive function/attention							
Digit span SS§ (n)	29	29	29	33	33	33	
Digit span backward	96 ± 3	92 ± 3	96 ± 2	94 ± 3	92 ± 2	92 ± 2	.23
Fluencies SS§	12	12	12	17	17	17	
Phonetic fluency	90 ± 4	93 ± 3	95 ± 3	94 ± 4	90 ± 3	91 ± 2	.36
Semantic fluency	97 ± 3	105 ± 4	99 ± 4	104 ± 5	98 ± 3	94 ± 3	.37
CPT SS§ (N)	32	32	32	31	31	31	
Omissions	82 ± 5	84 ± 4	88 ± 4	88 ± 4	80 ± 4	83 ± 4	.41
Commissions	97 ± 2	100 ± 3	101 ± 2	95 ± 3	98 ± 3	100 ± 2	.73
Hit react time	89 ± 3	87 ± 4	84 ± 3	90 ± 3	88 ± 4	80 ± 3	.40
Variability	87 ± 2	85 ± 2	86 ± 2	85 ± 2	84 ± 2	86 ± 2	.95
Perseverations	80 ± 5	72 ± 5	76 ± 5	72 ± 6	71 ± 5	74 ± 5	.78
Domain 4: social function							
CBCL *t* scores‡ (N)	35	35	35	36	36	36	
Behavior total	58 ± 2	57 ± 1	56 ± 1	60 ± 2	59 ± 1	59 ± 1	.16
Internalizing total	58 ± 2	55 ± 1	54 ± 1	57 ± 2	58 ± 1	57 ± 1	.10
Externalizing total	51 ± 2	52 ± 1	51 ± 1	55 ± 2	53 ± 1	54 ± 1	.24
Withdrawn	60 ± 2	56 ± 1	56 ± 1	57 ± 1	57 ± 1	57 ± 1	.34
Somatic complaints	60 ± 2	58 ± 1	56 ± 1	59 ± 1	59 ± 1	59 ± 1	.10
Anxious/depressed	58 ± 2	56 ± 1	55 ± 1	58 ± 2	59 ± 1	59 ± 1	.03
Social problems	60 ± 2	58 ± 1	59 ± 1	62 ± 2	61 ± 1	64 ± 1	.01
Thought problems	59 ± 2	56 ± 1	56 ± 1	56 ± 1	57 ± 1	56 ± 1	.81
Attention problems	63 ± 2	61 ± 1	60 ± 2	62 ± 2	65 ± 1	63 ± 2	.09
Delinquent behavior	55 ± 1	56 ± 1	55 ± 1	56 ± 1	56 ± 1	55 ± 1	.69
Aggressive behavior	55 ± 1	57 ± 1	55 ± 1	58 ± 2	56 ± 1	57 ± 1	.31
Sex problems	55 ± 1	55 ± 1	53 ± 1	55 ± 1	53 ± 1	52 ± 1	.52
Piers Harris SS§ (n)	16	16	16	20	20	20	
Behavioral adjustment	101 ± 4	104 ± 3	104 ± 3	102 ± 3	103 ± 2	102 ± 3	.71
Intellectual/school status	99 ± 4	100 ± 2	99 ± 3	101 ± 3	100 ± 2	97 ± 2	.51
Physical appearance	103 ± 3	103 ± 3	103 ± 3	105 ± 2	105 ± 2	105 ± 2	.56
Freedom from anxiety	97 ± 4	105 ± 3	106 ± 2	102 ± 3	102 ± 2	99 ± 2	.04
Popularity	94 ± 4	98 ± 3	100 ± 3	97 ± 3	98 ± 2	97 ± 3	.55
Happiness/satisfaction	103 ± 3	106 ± 2	107 ± 3	107 ± 2	105 ± 2	103 ± 2	.27
Total	99 ± 5	104 ± 3	105 ± 3	102 ± 3	103 ± 2	100 ± 2	.15
CDI *t* scores‡ (n)	15	15	15	21	21	21	
Total	47 ± 3	46 ± 1	45 ± 2	48 ± 2	48 ± 1	47 ± 2	.50
Negative mood	46 ± 2	46 ± 2	46 ± 2	48 ± 2	46 ± 1	47 ± 2	.60
Interpersonal problems	52 ± 3	48 ± 2	45 ± 2	48 ± 2	50 ± 1	50 ± 1	.02
Ineffectiveness	47 ± 2	47 ± 2	46 ± 2	49 ± 2	49 ± 2	50 ± 2	.13
Anhedonia	48 ± 3	50 ± 2	51 ± 2	51 ± 2	50 ± 2	50 ± 2	.74
Negative self-esteem	46 ± 2	43 ± 1	41 ± 1	46 ± 1	45 ± 1	44 ± 1	.08

PANESS, Physical and Neurological Evaluation for Soft Signs.
*ANCOVA LSM ± SE for change from baseline at 2 years, adjusted for differences in baseline value, age, SES.
†Unadjusted baseline values mean ± SEM.
‡Scores are expressed as *t* scores with mean of 50 and SD of 10. Lower scores imply better function and higher scores indicate more problem behaviors. For the CBCL, the 3 social competency scales are scored such that higher scores indicate better social competence.
§Scores are expressed as standard scores with mean of 100 and SD of 15. Higher scores imply better function.