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Moderators of Parent Training for Disruptive Behaviors in Young Children with Autism Spectrum Disorder

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Conflict of Interest

Author (d) serves as a consultant for The Autism Foundation. Author (j) serves as a consultant for the following research organizations: Neuren, Coronado, Roche and Supernus Pharmaceuticals. Additionally, author (j) receives royalties from Oxford and Guilford Press and receives research funds from The Marcus Foundation. Author (f) has received a research grant from The Autism Treatment Network (#UA3MC11054). Author (f) served as a consultant, served on the advisory board and participated in investigator training for: Cogstate, Inc., Confluence Pharmaceutica; Cogstate Clinical Trials, Ltd., Coronado Biosciences, Forest Research, Hoffman-La Roche, Lumos Pharma, Medavante, Inc., Novarti's, Pfizer, Prophase LLC and Supernus Pharmaceuticals. Author (b) has received research grants from HRSA, NIH, NIMH, Autism Speaks, U.S. Department of Education, NIH/UCLA and AIR-B/HRSA. All other authors have declared that they have no conflict of interest.

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Abstract

We conducted a 6 month, randomized trial of parent training (PT) versus a parent education program (PEP) in 180 young children (158 boys, 22 girls), ages 3–7 years, with autism spectrum disorder (ASD). PT was superior to PEP in decreasing disruptive and noncompliant behaviors. In the current study, we assess moderators of treatment response in this trial. Thirteen clinical and demographic variables were evaluated as potential moderators of three outcome variables: the Aberrant Behavior Checklist-Irritability subscale (ABC-I), Home Situations Questionnaire (HSQ), and Clinical Global Impressions-Improvement Scale (CGI-I). We used an intent-to-treat model and random effects regression. Neither IQ nor ASD severity moderated outcome on the selected outcome measures. Severity of Attention Deficit Hyperactivity Disorder (ADHD) and anxiety moderated outcomes on the ABC-I and HSQ. For instance, there was a 6.6 point difference on the ABC-I between high and low ADHD groups ($p = .05$) and a 5.3 point difference between high and low Anxiety groups ($p = .04$). Oppositional defiant disorder symptoms and household income moderated outcomes on the HSQ. None of the baseline variables moderated outcome on the CGI-I. That IQ and ASD symptom severity did not moderate outcome suggests that PT is likely to benefit a wide range of children with ASD and disruptive behavior.

Keywords

Autism spectrum disorder; parent training; moderator; ADHD; anxiety

Autism Spectrum Disorder (ASD) is a heterogeneous condition of early childhood onset defined by impaired social communication, repetitive behavior and restricted interests. Available evidence suggests that ASD affects approximately 6 per 1,000 children with about 30% functioning in the range of intellectual disability (Elsabbagh, Divan, Koh, Kim, Kauchali, Marcin, Montiel-Nava, Patel, Paula, Wang, Yasamy & Fombonne, 2012). Many children with ASD also exhibit behavioral problems such as tantrums, aggression, self-injury, hyperactivity, impulsiveness and noncompliance (Gadow, DeVincent, Pomeroy, Azizian, 2005; Kaat and Lecavalier, 2013). These co-occurring behavioral problems can pose enormous challenges to parents, lead to more restrictive school placements and the need for intensive behavioral interventions, medication or both.

Two medications, risperidone and aripiprazole, have demonstrated efficacy for the treatment of serious behavioral problems in children with ASD (Owen et al., 2009; Research Units on Pediatric Psychopharmacology [RUPP] Autism Network, 2002). Many parents and

clinicians, however, may be reluctant to use these potent drugs in young children. Interventions based on the principles of applied behavior analysis (ABA) also can help reduce behavior problems (Beavers et al., 2013; Wong et al., 2014). To date, most ABA studies in this population used individualized single-subject design studies. An emerging literature on the use of structured parent training (PT) in children with ASD and disruptive behavior offers encouraging results (McIntyre, 2008; Tonge, Brereton, Kiomall, Mackinnon & Rinehart, 2014). In children with disruptive behavior uncomplicated by ASD, PT is considered an evidenced-based intervention (Dretzke et al., 2009; Michelson, Daveport, Dretzke, Barlow & Day, 2013; Ollendick, Jarrett, Grills-Taquechel, Hovey & Wolf, 2008). The limited specialized resources amidst the growing number of children identified with ASD makes PT especially appealing.

In a prior publication, we showed that a structured PT intervention based on ABA principles was superior to a parent education program (PEP) in reducing disruptive and noncompliant behavior in young children with ASD (Bearss et al., 2015). This study of 180 children was the largest randomized controlled trial (RCT) to date of PT aimed at reducing behavior problems in ASD. Other strengths of the study included the 24-week duration, 24-week post-treatment follow-up, and use of PEP as an active comparator to control for therapist attention and maturation. After 24 weeks of treatment, PT was superior to PEP on the parent-rated Irritability subscale of the Aberrant Behavior Checklist (ABC; effect size = 0.62; $p < .001$) and the total Score of the Home Situations Questionnaire (HSQ; effect size = 0.45; $p < .001$). The positive response rates on the Clinical Global Impression-Improvement (CGI) scale completed by a masked rater were 68.5% for PT versus 39.6% for PEP ($p < .001$).

In this report, we focus on moderators of treatment outcome from this multisite RCT. Moderating variables are baseline characteristics that significantly affect the pre-specified primary and key secondary outcomes. The identification of moderators may provide insight on subgroups that may be more or less likely to respond to an efficacious treatment. To minimize type 1 error, we selected *a priori* candidate demographic and clinical variables that could have a prognostic influence on outcome. In terms of demographic variables, we focused on the child's IQ, socioeconomic status, and educational placement. We hypothesized that group differences favoring PT would be more pronounced in higher functioning children and those with less family adversity. In terms of clinical variables, we focused on the severity of co-occurring attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and anxiety, as well as the severity of ASD symptoms and compulsive behaviors. We hypothesized that group differences favoring PT would be more pronounced in children with milder comorbidities (ADHD, ODD, and anxiety) and less severe ASD symptoms. Selected variables were based on clinical consensus and prior research on behavioral interventions in children with ASD, ADHD, or ODD/CD (Beauchaine, Webster-Stratton & Reid, 2005; Chronis, Chacko, Fabiana, Wymbs & Pelham., 2004; Lundahl, Risser, Lovejoy, 2005; MTA Cooperative Group, 1999; Ollendick et al., 2008; Rogers, 1998).

Methods

Design

The background, methods, and main findings from the study have been reported elsewhere (Bearss et al., 2015). Briefly, the study was an RCT conducted at six sites (Emory University, Indiana University, Ohio State University, University of Pittsburgh, University of Rochester, Yale University). The trial was approved by the institutional review boards at each site. Informed consent was obtained from all individual participants included in the study. Eligible children were randomly assigned in 1:1 ratio to PT or PEP for 24 weeks using permuted blocks with concealed allocation to investigators. Parents and therapists were not blind to treatment. Assessments, completed every 4 weeks, included several parent ratings and interviews by an independent blinded clinician. At endpoint, the independent evaluator rated each child's treatment response as positive or not on the CGI-I. A positive response on the CGI-I was defined as a score of 1 (*Very Much Improved*) or 2 (*Much Improved*). Subjects and families in the PT group were invited to return for assessment at weeks 36 and 48 to evaluate longer-term outcomes. Parents received compensation to cover travel costs for each assessment and therapy visit. The study results, adverse events, enrollment and attrition were reviewed by an external data and safety monitoring board every 6 months.

Participants

One-hundred-eighty children between the ages of 3 and 7 years inclusive participated in the 24-week study targeting disruptive and noncompliant behaviors. Children were randomized to either the PT program or PEP. Inclusion criteria required an ASD diagnosis, a score > 15 on the Irritability subscale of the ABC (described below) and a CGI Severity (CGI-S) score > 4. Participants could take medication, as long as it had been stable for 6 weeks and there were no planned changes for the course of the study. Exclusion criteria encompassed any serious medical conditions or psychiatric disorder, receptive language skills < 18 months, and current or past enrollment in structured PT. Clinical diagnosis of ASD was made according to DSM-IV-TR criteria (American Psychiatric Association, 2000), based on a comprehensive clinical assessment and corroborated by the Autism Diagnostic Interview-Revised (ADI-R; Rutter, Le Couteur & Lord, 2003) and Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000) completed by clinicians trained to reliability.

Measures

Outcome measures—Aberrant Behavior Checklist (ABC; Aman, Singh, Stewart, & Field, 1985a; Aman, Singh, Stewart & Field, 1985b) is a 58-item rating scale. Each item is rated on a Likert scale from 0 (*not a problem*) to 3 (*severe in degree*). The ABC contains five subscales: I) Irritability (15 items), II) Social Withdrawal (16 items), III) Stereotypic Behavior (7 items), V) Hyperactivity/Noncompliance (16 items), and V) Inappropriate Speech (4 items). The ABC is reliable, valid, and sensitive to treatment effects in ASD (Kaat, Aman, Lecavalier, 2014). It was completed at baseline and every 4 weeks thereafter.

Home Situations Questionnaire – Autism Spectrum Disorder (HSQ) is a 24-item parent rating scale that assesses noncompliance. Parents are asked to indicate whether or not each

item is a problem and, if so, to rate its severity on a Likert scale from 1 (*mild*) to 9 (*severe*). Originally developed as a measure of disruptive behavior in children with Attention Deficit Hyperactive Disorder (Barkley & Edelbrock, 1987), it was adapted by the RUPP Autism Network to evaluate noncompliance in children with ASD (Chowdhury et al., 2015). We report average per item score. It was completed at baseline and every 4 weeks thereafter.

Clinical Global Impressions - Improvement Scale (CGI; Guy 1976) is a 7-point scale designed to measure overall improvement from baseline. Scores range from 1 (*very much improved*) through 4 (*unchanged*) to 7 (*very much worse*). Scores of 1 or 2 identified clinical responders. A blinded evaluator completed the CGI-I every 4 weeks after baseline.

Moderator variables—Early Childhood Inventory (ECI; Sprafkin, Volpe, Gadow, Nolan & Kelly, 2002) is a DSM-IV-referenced, parent report of child behavior. Items are scored from 0 (*never*) to 3 (*very often*) and can be scored in two different ways: symptom count (number of items rated 2 or 3) and symptom severity (sum of the scores for the specific diagnostic subscale). The scale has been shown to be valid in young children with ASD (Lecavalier, Gadow, DeVincenzo, Houts & Edwards, 2011). Of interest in the current study were the following subscales: attention-deficit/hyperactivity disorder (ADHD; 18 items), oppositional defiant disorder (ODD; 8 items), pervasive developmental disorder (PDD; 12 items), and 16-items measuring anxiety (Hallett et al., 2013). The ADHD subscale was used dimensionally (i.e., symptom severity) and categorically (i.e., symptom count in accordance with DSM-IV).

Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000) is an investigator-based assessment conducted in naturalistic social situations demanding specific social, communication and restricted/repetitive responses. Behaviors are scored in the areas of social communication, social relatedness, play and imagination, and repetitive behaviors. This measure was used to support the clinical diagnosis and provides a severity score.

Children's Yale-Brown Obsessive-Compulsive Scales-*PDD* (CYBOCS-PDD; Scahill et al., 2006). The CYBOCS-PDD is a modified version of the CYBOCS developed for use in children with Obsessive Compulsive Disorder (Scahill et al., 1997). The modified version is a semi-structured clinician-rated scale designed to rate the current severity of repetitive behavior in children with ASD (Scahill et al., 2006). Current repetitive behaviors are rated on 5 dimensions: Time Spent, Interference, Distress, Resistance, and Control. Each dimension is scored on a 5-point scale from 0 (*least symptomatic*) to 4 (*most symptomatic*), yielding a Total score from 0 to 20. The CYBOCS-PDD has established reliability and validity and is sensitive to change in ASD.

Developmental/Cognitive functioning: The Stanford-Binet Fifth Edition (SB-V; Roid, 2003) or the Mullen's Scale of Early Learning (MSEL; Mullen, 1995) were used according to the developmental level of the child. The SB-V was attempted with all children, and, whenever possible, the abbreviated version was completed. The Mullen was administered to the minority of children who did not achieve a basal score on the SB-V because of limited language skills or mental age below 2–3 years.

Treatments

The PT consisted of 11 sessions delivered individually and included direct instruction, video vignettes, role playing, and homework to be completed between sessions. Sessions lasted 75–90 minutes. Parents were educated on behavioral principles and on a host of behavioral intervention strategies such as use of visual cues and reinforcement, as well as the teaching of compliance and other adaptive skills (Bearss, Johnson, Handen et al., 2015). The PEP consisted of 12 individually-delivered that covered useful topics for parents of young children with ASD, including etiology of ASD, educational planning, advocacy, and selecting effective treatments (see Bearss et al., 2015). PEP sessions were the same duration as PT sessions. PEP was chosen as an active comparison group to control for time and therapist attention, allowing us to determine if information alone would improve behavior problems.

Data Analysis

To minimize type 1 error, we selected variables *a priori* as candidates that could influence outcome. Demographic variables included ethnicity, socioeconomic status, maternal education and intact family constitution or not. Child variables included educational placement, estimated IQ (< 70 or ≥ 70) as well as severity indices of ASD, ADHD, ODD, anxiety and repetitive behavior.

Random effects regression, including random effects for intercept and slope and fixed effects for baseline outcome variable, treatment (PT or PEP), time (as a continuous variable), site, educational intensity, and the interaction between time and treatment, was used in the original trial analysis. In the current analysis, similar models were employed adding fixed effects for the putative moderator variables and the interactions of moderators, treatment and time. No significant two-way interactions of moderators by treatment were observed demonstrating that moderation of treatment differences required follow-up time to develop. This was evaluated using three-way interactions (moderator by treatment by time) which evaluate whether the treatment difference in the *rate of change* for an outcome was dependent on the moderator variable.

To illustrate the moderation effect, the least squares mean treatment difference and 95% confidence interval at the week 24 endpoint was generated for each level of moderator variable and was presented in a forest plot. Statistical significance of moderators measured on a continuous scale was evaluated using the continuous variable. For ease of presentation and interpretation, continuous moderators were split above and below the 75th percentile to demonstrate differences in magnitudes of treatment effects across the moderator.

All analyses were performed using SAS 9.4 (Cary, NC) and statistical significance evaluated at the two-sided 0.05 significance level.

Results

Table 1 summarizes baseline demographic and clinical characteristics. It was not possible to estimate IQ for 17 children who did not complete the SB-5 or the Mullen subtests. Of these, 15 children did complete the Mullen Receptive Language subtest to confirm the > 18-month

receptive language entry criterion. Based on their Receptive Language T-scores, a panel of psychologists classified these subjects as $IQ < 70$ ($n = 10$ in PT; $n = 5$ in PEP) for analytic purposes. The remaining two children could not be tested; they were allowed to enter the study following individual case reviews by senior investigators and were not classified as above or below 70.

Figure 1 shows forest plots for potential moderators with the ABC-I as the outcome measure. The X-axis represents treatment differences in ABC-I (PT minus PEP) at week 24 whereby negative scores indicated a better treatment response in PT than PEP (i.e. ABC-I scores were lower in PT at 24 weeks compared to PEP). For continuous moderators, the red circles represent children in the top quartile (above the 75th percentile), while the blue squares represent children in the lower three quartiles (at or below the 75th percentile). ADHD total score ($p = 0.05$), ABC hyperactivity score ($p = 0.03$), ECI-anxiety ($p = 0.04$) and ECI categorized probable ADHD ($p = 0.01$) significantly moderated the treatment response. The benefit of PT was significantly greater for those with lower ADHD scores, treatment difference = -5.54 , 95% confidence interval (CI) $[-8.06 - -3.02]$; compared to those with higher scores, 1.13 , 95% CI $[-3.66 - 5.93]$. Those with lower ABC hyperactivity had a greater PT benefit, -4.96 ; 95% CI $[-7.46, -2.46]$ compared to those with higher scores, -0.37 , CI 95% $[-5.15 - 4.41]$. The difference between PT and PEP was also more pronounced in those with lower ECI-anxiety scores, -5.26 , 95% CI $[-7.8 - -2.67]$ compared to those with higher scores, 0.005 ($-4.45 - 4.46$). Finally, when the ECI was used to classify children with or without probable ADHD, children with probable ADHD showed no difference between treatment groups, -0.65 , 95% CI $[-4.19 - 2.90]$ on ABC-I. Children without probable ADHD showed greater PT benefit -6.29 , 95% CI $[-9.10 - -3.47]$.

Figure 2 shows forest plots for potential moderators with the HSQ as the outcome measure. These plots are to be interpreted in the same way as Figure 1. Treatment differences were significantly modified by ECI-ODD ($p = 0.05$), ECI-anxiety ($p = 0.01$), ECI-categorized probable ADHD ($p = 0.03$), and household income ($p = 0.01$). The magnitude of the PT effect was greater in those with lower $[-0.91 (-1.37, -0.45)]$ compared to higher ODD symptoms $[-0.16 (-1.01, 0.70)]$; lower $[-0.92 (-1.38, -0.45)]$ compared to higher ECI-anxiety scores $[-0.05 (-0.86, 0.75)]$; those without $[-1.02 (-1.54, -0.51)]$ compared to with ECI categorized probable ADHD $[-0.25 (-0.90, 0.39)]$ and when household income was above $[-0.88 (-1.35, -0.40)]$ compared to below \$40,000 $[-0.15 (-0.91, 0.61)]$. Although these factors moderated the treatment effect of PT compared to PEP, there was evidence of improvement in PT and PEP in children with higher levels of oppositional behavior, ADHD symptom and anxiety. For example, treatment difference in ABC-I scores from baseline to week 24 were -10.3 and -11.9 for high-ECI ADHD groups in PT and PEP, respectively. Likewise, treatment difference in HSQ scores from baseline to week 24 were -2.4 and -2.1 for high-ECI ODD groups in PT and PEP, respectively. Similarly, treatment difference in HSQ scores from baseline to week 24 were -2.3 and -2.7 for high-ECI anxiety groups in PT and PEP, respectively.

Figure 3 shows forest plots for moderator variables with the CGI-I as the outcome measure. The X-axis is the odds ratio of positive response (much improved or very much improved) of PT compared to PEP. Analyses from the original trial showed a significantly higher rate of

positive response in PT compared to the PEP group. However, none of the moderators evaluated here significantly modified the likelihood of positive response between PT and PEP on the CGI-I.

Discussion

These analyses showed that ADHD and anxiety symptom-severity moderated outcome on both the ABC-I and the HSQ. In children with lower parent-rated symptoms of ADHD and anxiety on the ECI, there was a significantly greater difference in PT on the ABC-I and HSQ compared to PEP. This finding was evident with both dimensional and categorical scores for ADHD on the ABC-I, where the difference between high and low ADHD groups was about 6 points. As reported in Bearss et al., (2015) the treatment difference between PT and PEP was 4.6 points on the ABC-I. These results indicate that the significant difference between groups was driven by the change in the children with lower levels of hyperactivity. Nonetheless, children with higher ADHD scores showed improvement on the ABC-I and HSQ. The benefits were roughly equal for PT and PEP.

Hyperactivity, impulsiveness and distractibility are common co-occurring problems in children with ASD (Simonoff et al., 2008). Children with ASD plus ADHD show lower rates of positive response to ADHD medications compared to children ADHD without ASD (RUPP Autism Network, 2005; Scahill et al., 2015). These children may also have greater adaptive skill deficits relative to their cognitive abilities than children who have ASD without ADHD (Ashwood et al., 2015).

There is evidence for the efficacy of behavioral PT for ADHD in children without ASD (Lee, Niew, Yang, Chen & Lin, 2012; Ollendick et al., 2008). This seems to be particularly true in preschoolers (Webster-Stratton, Reid & Beauchaine, 2011; Jones, Daley, Hutchings, Bywater & Eames, 2007). However, some studies have reported no benefits of PT on symptoms of ADHD (e.g., Van Den Hoofdakker et al., 2003). The evidence is not as clear and consistent as the evidence for PT in ODD/CD without ADHD (Dretzke et al., 2009; Michelson et al., 2013; Webster-Stratton et al., 2011). Indeed, severe hyperactivity and impulsiveness seem to present a greater challenge for the application of behavior management techniques.

A trial of atomoxetine and PT in 128 children (mean age 8 years) with ASD and ADHD is relevant to the current findings (Handen et al., 2015). In this study, children were randomized to one of four conditions: drug only, drug and PT, placebo, or PT with pill placebo. This 10-week study used a briefer, but similar PT program. On the HSQ, the PT group showed less improvement than the atomoxetine group, and was not significantly different from the placebo group. The results of this study also suggest that ADHD symptoms presents additional treatment challenges in children with ASD.

The presence of higher parent ratings of anxiety also predicted a smaller treatment effect for PT compared to PEP on both the ABC-I and the HSQ. Others have suggested that low-anxiety children with disruptive behavior problems may be optimally responsive to interventions that focus on altering instrumental operant contingencies within the home

(Beauchaine et al., 2005). Along these lines, Pincus, Santucci, Ehrenreich and Eyeberg, (2008) found that Parent-Child Interaction Therapy without modifications was not effective as a stand-alone treatment to reduce childhood anxiety (n = 10; average age = 6 years). Although the current PT was not designed to target anxiety symptoms, it may be that more severe anxiety symptoms interfere with the treatment of disruptive and noncompliant behaviors. Similarly, disruptive and noncompliant behaviors could stem from anxiety rather than ASD (Bearss et al., 2016). This has been documented in children without ASD, where improvement in anxiety mediated improvement in disruptive behaviors (Arnold et al., 2015).

On balance, however, these results do not imply that children with ADHD or anxiety symptoms will not benefit from PT. For example, the likelihood of positive response on the CGI-I were not different across high- and low- ADHD or anxiety groups. Moreover, potentially relevant moderators such as IQ and ASD severity were not significant, suggesting that PT will benefit children with a range of impairments. Our examination of socioeconomic metric such as parent education, two-parent family, and household income was limited by the lack of variability in our sample. Nevertheless, only one of the nine analyses was significant (household income moderated outcome on the HSQ). In contrast, a number of socioeconomic status variables such as single parent status, young parent age, unstable housing, and reliance on government subsidies have been associated with poorer PT outcome in children without ASD (Lundahl et al., 2005). Socioeconomic adversity could undermine the efficacy of PT by disrupting the implementation of the intervention. Further study is needed to explore the application of PT in lower socioeconomic groups and rural samples.

Our results should be interpreted with a few caveats. Although this study is the largest to date of a behavioral intervention in children with ASD, the sample is rather small given the number of comparisons. The study of moderators was not the primary objective of the trial and therefore was exploratory in nature and requires replication. In addition, the significant associations were based on parent ratings who were not blinded to treatment assignment.

The results of the current study may inform the sequencing of treatment for children with ASD and disruptive behavior problems. Children with prominent symptoms of ADHD or anxiety may need treatments to target these areas prior to initiating PT.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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References

- Aman MG, Singh NN, Stewart AW, Field CJ. The Aberrant Behavior Checklist: A behavior rating scale for the assessment of treatment effects. *American Journal of Mental Deficiency*. 1985a; 89:485–491. [PubMed: 3993694]
- Aman MG, Singh NN, Stewart AW, Field CJ. Psychometric characteristics of the Aberrant Behavior Checklist. *American Journal of Mental Deficiency*. 1985b; 89:492–502. [PubMed: 3158201]
- American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-IV-TR*. Washington, DC: American Psychiatric Association; 2000.
- Arnold LE, Gadow KD, Farmer CA, Findling RL, Bukstein O, Molina BG, ... Aman MG. Comorbid anxiety and social avoidance in treatment of severe childhood aggression: Response to adding risperidone to stimulant and parent training; Mediation of disruptive symptom response. *Journal of Child and Adolescent Psychopharmacology*. 2015; 25:203–212. [PubMed: 25885010]
- Ashwood KL, Tye C, Azadi B, Cartwright S, Asherson P, Bolton P. Brief report: Adaptive functioning in children with ASD, ADHD, and ASD + ADHD. *Journal of Autism and Developmental Disorders*. 2015; 45:2235–2242. [PubMed: 25614019]
- Barkley, RA., Edlbrock, C. Assessing situational variation in children's problem behaviors: The Home and School Situations Questionnaires. In: Prinz, R., editor. *Advances in Behavioral Assessment of Children and Families* (. Greenwich, CT: JAI Press Inc; 1987. p. 157-176.
- Bearss, K., Johnson, C., Handen, B., Butter, E., Lecavalier, L., Smith, T., Scahill, L. *RUBI Autism Network: Parent Training for Disruptive Behavior [A Treatment Manual]*. Authors; 2015.
- Bearss K, Johnson C, Smith T, Lecavalier L, Swiezy N, ... Scahill L. Parent training for young children with autism spectrum disorder and disruptive behavior: A randomized clinical trial. *Journal of the American Medical Association*. 2015; 313:1524–1533. [PubMed: 25898050]
- Bearss K, Taylor CA, Aman MG, Whittmore, Lecavalier L, ... Scahill L. Using qualitative methods to guide scale development for anxiety in autism spectrum disorder. *Autism*. 2016; 20:663–672. [PubMed: 26395234]
- Beauchaine TP, Webster-Stratton C, Reid MJ. Mediators, moderators, and predictors of 1-year outcomes among children treated for early-onset conduct problems: A latent growth curve analysis. *Journal of Consulting and Clinical Psychology*. 2005; 73:371–388. [PubMed: 15982136]
- Beavers GA, Iwata BA, Lerman DC. Thirty years of research on the functional analysis of problem behavior. *Journal of Applied Behavior Analysis*. 2013; 46:1–21. [PubMed: 24114081]
- Chowdhury M, Aman M, Lecavalier L, Smith T, Johnson C, ... Scahill L. Factor structure and psychometric properties of the Home Situations Questionnaire for autism spectrum disorder: The Home Situations Questionnaire – Autism Spectrum Disorder. *Autism*. 2015; 20:528–537. [PubMed: 26187059]
- Chronis AM, Chacko A, Fabiano GA, Wymbs BT, Pelham WE. Enhancements to the Behavioral Parent Training Paradigm for Families of Children With ADHD: Review and Future Directions. *Clinical Child and Family Psychology Review*. 2004; 7:1–27. [PubMed: 15119686]
- Dretzke J, Davenport C, Frew E, Barlow J, Stewart-Brown S, Bayliss S, ... Hyde C. The clinical effectiveness of different parenting programmes for children with conduct problems: a systematic review of randomised controlled trials. *Child and Adolescent Psychiatry and Mental Health*. 2009; 3(7)
- Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S, Marcin C, ... Fombonne E. Global Prevalence of Autism and Other Pervasive Developmental Disorders. *Autism Research*. 2012; 5:160–179. [PubMed: 22495912]

- Gadow KD, DeVincent CJ, Pomeroy J, Azizian A. Psychiatric symptoms in preschool children with PDD and clinic and comparison samples. *Journal of Autism and Developmental Disorders*. 2005; 34:379–393.
- Guy, W. US Dept Health, Education, and Welfare publication (ADM). ECDEU Assessment Manual for Psychopharmacology. Rockville, Md, USA: National Institute of Mental Health; 1976. p. 218-222. Clinical global impression (C.G.I.)
- Hallett V, Lecavalier L, Sukhodolsky DG, Cipriano N, Aman MG, McCracken JT, ... Scahill L. Exploring anxiety in children with Pervasive Developmental Disorders across a broad range of functioning. *Journal of Autism and Developmental Disorders*. 2013; 10:2341–2352.
- Handen BL, Aman MG, Arnold LE, Hyman SL, Tumuluru RV, Lecavalier L, ... Smith T. Effects of Atomoxetine, parent training, and their combination in children with autism spectrum disorder and ADHD symptoms. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2015; 54:905–915. [PubMed: 26506581]
- Jones K, Daley D, Hutchings J, Bywater T, Eames C. Efficacy of the Incredible Years Basic parent training programme as an early intervention for children with conduct problems and ADHD. *Child: Care, Health and Development*. 2007; 33(6):749–756.
- Kaat AJ, Lecavalier L. Disruptive behavior disorders in children and adolescents with autism spectrum disorders: a review of the prevalence, presentation, and treatment. *Research in Autism Spectrum Disorders*. 2013; 7:1579–1594.
- Kaat AJ, Lecavalier L, Aman MG. Validity of the Aberrant Behavior Checklist in children with autism spectrum disorders. *Journal of Autism and Developmental Disorders*. 2014; 44:1103–1116. [PubMed: 24165702]
- Lecavalier L, Gadow KD, DeVincent CJ, Houts C, Edwards MC. Validity of DSM-IV syndromes in preschoolers with autism spectrum disorders. *Autism*. 2011; 15:527–543. [PubMed: 21454388]
- Lord C, Risi S, Lambrecht L, Cook EH, Leventhal BL, DiLavore PC, et al. The Autism Diagnostic Observation Schedule-Generic: A standard measure of social and communication deficits associated with the spectrum of autism. *Journal of Autism and Developmental Disorders*. 2000; 30:205–223. [PubMed: 11055457]
- Lee P, Niew W, Yang H, Chen VC, Lin K. A meta-analysis of behavioral parent training for children with attention deficit hyperactivity disorder. *Research in Developmental Disabilities*. 2012; 33:2040–2049. [PubMed: 22750360]
- Lundahl B, Risser HJ, Lovejoy MC. A meta-analysis of parent training: Moderators and follow-up effects. *Clinical Psychology Review*. 2005; 26:86–104. [PubMed: 16280191]
- Mandell DS, Morales KH, Marcus SC, Stahmer AC, Doshi J, Polsky DE. Psychotropic medication use among Medicaid-enrolled children with autism spectrum disorder. *Pediatrics*. 2008; 121:e441–e448. [PubMed: 18310165]
- McIntyre LL. Parent training for young children with developmental disabilities: Randomized controlled trial. *American Journal on Mental Retardation*. 2008; 113:356–368. [PubMed: 18702556]
- Michelson D, Daveport C, Dretzke J, Barlow J, Day C. Do evidence-based interventions work when tested in the “real world?” A systematic review and meta-analysis of parent management training for the treatment of child disruptive behavior. *Clinical Child and Family Psychology Review*. 2013; 16:18–34.
- MTA Cooperative Group. Moderators and mediators of treatment response for children with attention deficit/hyperactivity disorder. *Archives of General Psychiatry*. 1999; 56:1088–1096. [PubMed: 10591284]
- Mullen, E. Mullen Scales of Early Learning. Circle Pines: American Guidance Service; 1995. AGS Edition
- Ollendick TH, Jarrett MA, Grills-Taquechel AE, Hovey LD, Wolf JC. Comorbidity as a predictor and moderator of treatment outcome in youth with anxiety, affective, attention deficit/hyperactivity disorder, and oppositional/conduct disorders. *Clinical Psychology Review*. 2008; 28:1447–1471. [PubMed: 18973971]
- Owen R, Sikich L, Marcus RN, Corey-Lisle P, Manos G, McQuade RD, ... Findling RH. A multicenter, double-blind, randomized, placebo controlled, flexible-dose, parallel-group study of

- aripiprazole in the treatment of irritability in children and adolescents (6–17 years) with autistic disorder. *Pediatrics*. 2009; 124:1533–1540. [PubMed: 19948625]
- Pincus DB, Santucci LC, Ehrenreich JT, Eyberg SM. The implementation of modified parent-child interaction therapy for youth with separation anxiety disorder. *Cognitive and Behavioral Practice*. 2008; 15:118–125.
- Research Units on Pediatric Psychopharmacology (RUPP) Autism Network. Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. *Archives of General Psychiatry*. 2005; 62:1266–1274. [PubMed: 16275814]
- Roid, GH. *Stanford-Binet Intelligence Scales*. 5. Itasca, IL: Riverside; 2003.
- Rogers SJ. Empirically supported comprehensive treatments for young children with autism. *Journal of Clinical Child Psychology*. 1998; 27:168–179. [PubMed: 9648034]
- Rutter, M., Le Couteur, A., Lord, C. *Autism Diagnostic Interview Revised*. Torrance, CA: Western Psychological Services; 2003.
- RUPP Autism Network. Risperidone in children with autism and serious behavioral problems. *New England Journal of Medicine*. 2002; 347:314–321. [PubMed: 12151468]
- Scahill L, McDougle CJ, Williams SK, Dimitriopoulos A, Aman MG, et al. The Children's Yale–Brown Obsessive Compulsive Scales modified for pervasive developmental disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2006; 45:1114–1123. [PubMed: 16926619]
- Scahill L, McCracken JT, King BH, Rockhill C, Shah B, ... McDougle CJ. Research Units on Pediatric Psychopharmacology Autism Network. Extended-release guanfacine for hyperactivity in children with autism spectrum disorder. *American Journal of Psychiatry*. 2015; 172:1197–1206. [PubMed: 26315981]
- Scahill L, Riddle MA, McSwiggin-Hardin M, Ort SI, King RA, ... Leckman JF. Children's Yale–Brown Obsessive Compulsive Scale: reliability and validity. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1997; 36:844–852. [PubMed: 9183141]
- Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G. Psychiatric disorders in children with autism spectrum disorders: Prevalence, comorbidity, and associated factors in a population-derived sample. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2008; 47:921–929. [PubMed: 18645422]
- Sprafkin J, Volpe RJ, Gadow KD, Nolan EE, Kelly K. A DSM-IV- referenced screening instrument for preschool children: The Early Childhood Inventory- 4. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2002; 41:604–612. [PubMed: 12014793]
- Tonge B, Brereton A, Kiomall M, Mackinnon A, Rinehart NJ. A randomised group comparison controlled trial of 'preschoolers with autism': a parent education and skills training intervention for young children with autistic disorder. *Autism*. 2014; 18(2):166–177. [PubMed: 22987897]
- Van Den Hoofdakker BJ, Van der Veen-Mulder L, Sytema S, Emmelkamp PMG, Minderaa RB, Nauta MH. Effectiveness of Behavioral Parent Training for Children With ADHD in Routine Clinical Practice: A Randomized Controlled Study. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2007; 46:1263–1271. [PubMed: 17885567]
- Webster-Stratton CH, Reid MJ, Beauchaine T. Combining Parent and Child Training for Young Children with ADHD. *Journal of Clinical Child & Adolescent Psychology*. 2011; 40:191–203. [PubMed: 21391017]
- Wong, C., Odom, SL., Hume, K., Cox, AW., Fettig, A., Kucharczyk, S., ... Schultz, TR. Evidence-based practices for children, youth, and young adults with Autism Spectrum Disorder. Chapel Hill: The University of North Carolina, Frank Porter Graham Child Development Institute, Autism Evidence-Based Practice Review Group; 2014.

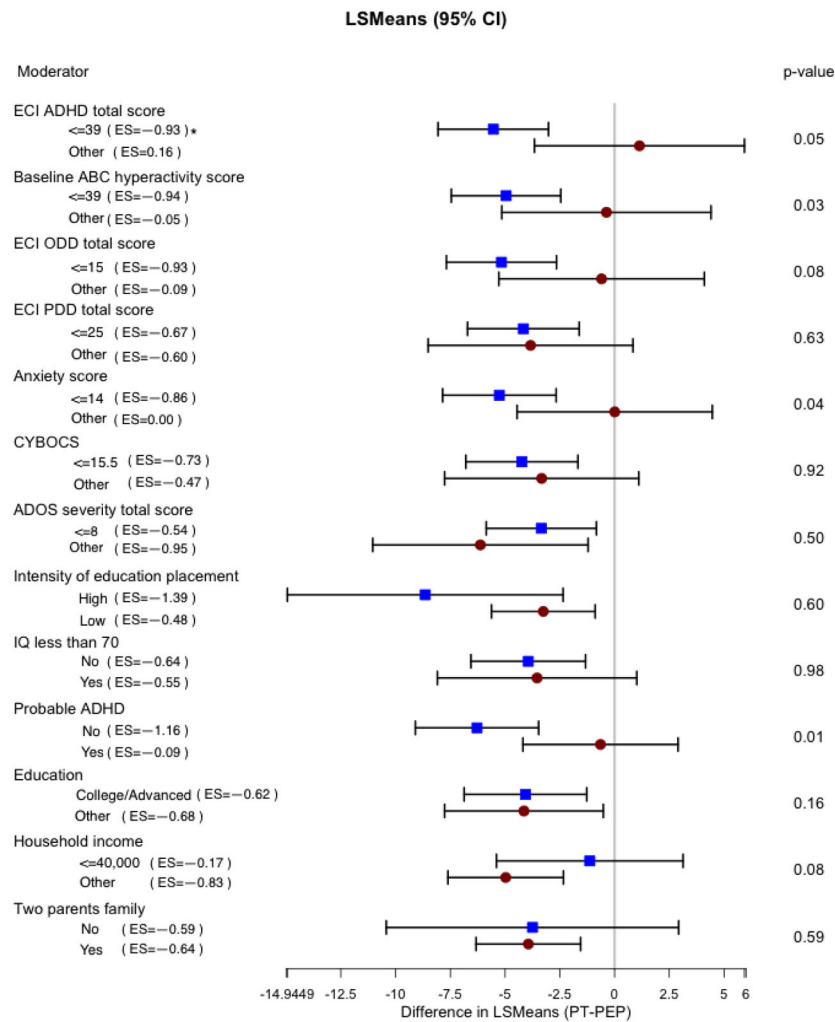


Figure 1. Forest plots showing differences in ABC-irritability scores between PT and PEP by moderator variables at the week 24 endpoint. P-values are from 3-way interactions of treatment by time by moderator
 ECI early childhood inventory, ES effect size, ABC aberrant behavior checklist, PDD pervasive developmental disorder, CYBOCS-PDD Children’s Yale-Brown Obsessive Compulsive Scale, ADOS Autism Diagnostic Observational Schedule, ADHD attention deficit hyperactivity disorder. For continuous variables, the red circle corresponds to the top quartile, while the blue squares correspond to the lowest three quartiles. In general, greater separation of the circle and the square suggest different responses for children scoring high and low, respectively, on the potential moderator. As the circle and square become closer together, the likelihood that the variable is a moderator declines. Effect size estimated by the difference in the least squares means at week 24 divided by the pooled standard deviation at baseline for the entire study sample.

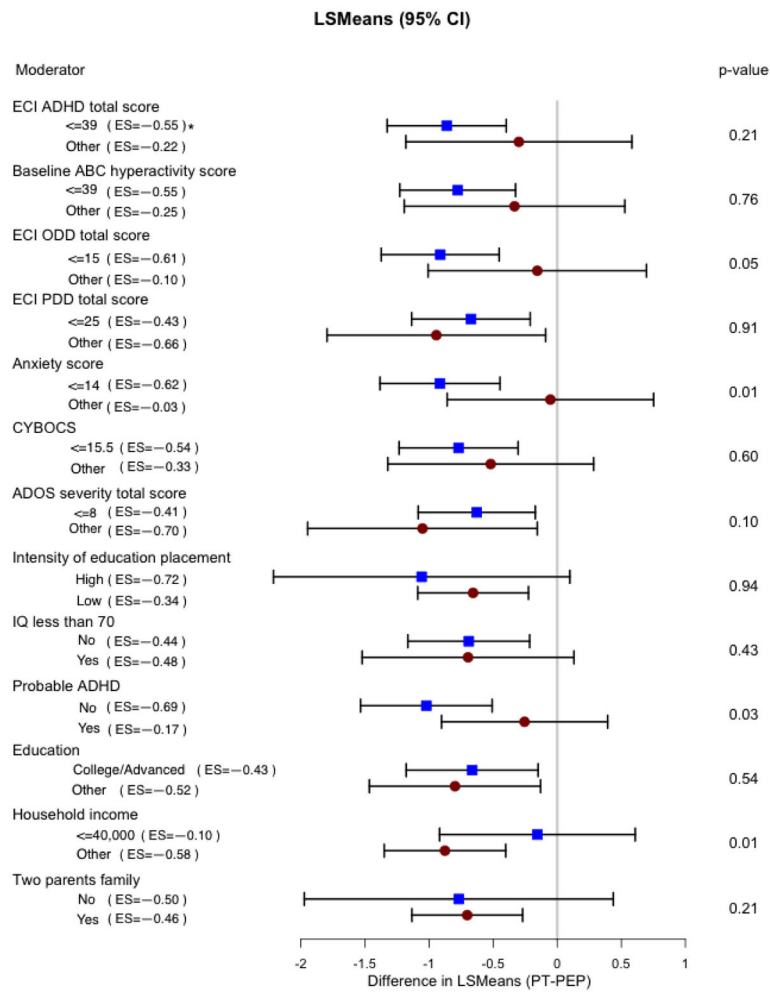


Figure 2. Forest plots showing differences in HSQ scores between PT and PEP by moderator variables at the week 24 endpoint. P-values are from 3-way interactions of treatment by time by moderator

ECI early childhood inventory, ES effect size, ABC aberrant behavior checklist, PDD pervasive developmental disorder, CYBOCS-PDD Children’s Yale-Brown Obsessive Compulsive Scale, ADOS Autism Diagnostic Observational Schedule, ADHD attention deficit hyperactivity disorder For continuous variables, the red circle corresponds to the top quartile, while the blue squares correspond to the lowest three quartiles. In general, greater separation of the circle and the square suggest different responses for children scoring high and low, respectively, on the potential moderator. As the circle and square become closer together, the likelihood that the variable is a moderator declines. Effect size estimated by the difference in the least squares means at week 24 divided by the pooled standard deviation at baseline for the entire study sample.

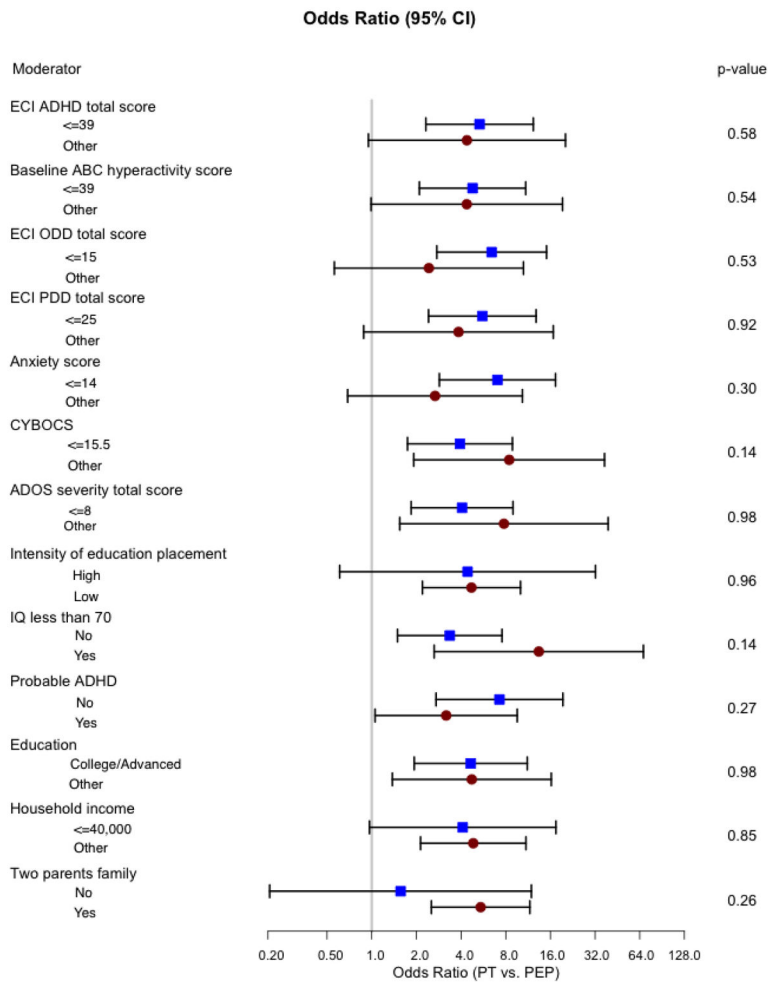


Figure 3. Forest plots comparing the likelihood of treatment response on CGI-I between PT and PEP by moderator variables at the week 24 endpoint. P-values are from 3-way interactions of treatment by time by moderator.

ECI early childhood inventory, ES effect size, ABC aberrant behavior checklist, PDD pervasive developmental disorder, CYBOCS-PDD Children’s Yale-Brown Obsessive Compulsive Scale, ADOS Autism Diagnostic Observational Schedule, ADHD attention deficit hyperactivity disorder. For continuous variables, the red circle corresponds to the top quartile, while the blue squares correspond to the lowest three quartiles. In general, greater separation of the circle and the square suggest different responses for children scoring high and low, respectively, on the potential moderator. As the circle and square become closer together, the likelihood that the variable is a moderator declines.

Table 1

Baseline Demographic and Clinical Characteristics of PT and PEP (N=180)

	PT (n = 89)		PEP (n = 91)		P value ^e
	N	%	N	%	
Child Demographics					
Age (mean, SD)	4.8	1.2	4.7	1.1	0.41
Males	79	88.8	79	86.8	0.82
IQ <70	13	14.6	16	17.6	0.69
70	67	74.2	67	74.7	
Missing ^a	10	11.2	7	7.7	
Race					
White	78	87.6	78	85.7	0.43
Black	9	10.1	6	6.6	
Ethnicity					
Hispanic	13	14.6	13	14.3	0.99
Nonhispanic	76	85.4	78	85.7	
DSM-IV Diagnosis					
Autistic Disorder	60	67.4	65	71.4	0.69
PDD – NOS	27	30.3	23	25.3	
Asperger's Disorder	2	2.3	3	3.3	
Taking Medicines					
Melatonin	9	10.1	9	9.9	0.27
Psychotropic	4	4.5	1	1.1	
Melatonin and psychotropic	4	4.5	4	4.4	
2 Psychotropics	4	4.5	1	1.1	
School Program					
Regular Class	36	40.0	46	50.5	0.51
Special Education Class	38	42.7	32	35.2	
Special Education School	13	14.6	10	11.0	
Home Instruction	2	2.2	3	3.3	
Parent Demographics					
					0.65

	PT (n = 89)		PEP (n = 91)		P value ^e
	N	%	N	%	
Two parent family	77	86.5	81	89.0	0.13
Maternal Education					
Advanced Degree	29	32.6	23	25.3	
College Degree ^b	22	24.7	37	40.7	
Some College	28	31.5	26	28.6	
High School Graduate	9	10.1	5	5.5	
Some High School	1	1.1	0	0.0	
Household income ^c					0.62
\$40,000	27	31	24	26	
Above \$40,000	61	69	67	74	
Baseline Clinical Scores					0.35
CGI-Severity					
Moderately III	32	36.0	32	35.2	
Markedly III	41	46.1	49	53.9	
Severely III	16	18.0	10	11.0	
	Mean	SD	Mean	SD	
Aberrant Behavior Checklist					
Irritability	23.7	6.4	23.9	6.2	0.85
Social Withdrawal	13.2	8.4	12.6	8.0	0.63
Stereotypy	6.2	4.8	6.6	5.1	0.57
Hyperactivity	29.5	9.8	31.4	8.7	0.19
Inappropriate Speech	5.3	3.1	6.1	3.2	0.12
ADOS					
Social affect and restricted and repetitive behavior total score	14.70	4.52	15.47	4.58	0.26
Home Situations Questionnaire-ASD					
Total	4.0	1.6	3.8	1.5	0.37
Vineland II Adaptive Scales					
Communication	80.4	15.1	82.2	15.6	0.43
Daily Living Skills	76.7	12.7	79.5	14.3	0.16
Socialization	70.5	11.3	73.5	10.5	0.07

	PT (n = 89)		PEP (n = 91)		P value ^e
	N	%	N	%	
Adaptive Behavior Composite	73.5	10.9	76.7	11.8	0.06
CYBOCS-PDD Total Score	13.42	3.28	13.22	3.73	0.71
Early Childhood Inventory					
ADHD	32.52	9.71	32.91	8.08	0.77
Above clinical cutoff (n,%) ^d	33	37	37	42	
ODD	11.88	5.76	11.32	5.55	0.51
Anxiety	11.39	7.24	11.26	6.31	0.90
PDD	20.89	6.66	20.17	6.79	0.48

^aPT Parent Training, PEP Psychoeducational Program, ADOS Autism Diagnostic Observational Schedule, CYBOCS-PDD Children's Yale-Brown Obsessive Compulsive Scale, ADHD attention deficit hyperactivity disorder, ODD oppositional defiant disorder, PDD pervasive developmental disorder. 17 children with missing IQ were untestable. 15 of 17 completed the Mullen Receptive Language (RL) scale to confirm RL >18 months. The remaining two children were deemed eligible by study case panel.

^bMaternal college degree greater in PEP (p < .05). There were no other significant between-group differences at baseline.

^cHousehold income missing on one family assigned to PT.

^dMissing data for three children in PEP group. Fisher's exact test was used for categorical variables and t test was used for continuous variables.