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Medication and Parent Training in Children with Pervasive Developmental Disorders and Serious Behavior Problems: Results from a Randomized Clinical Trial

Research Units on Pediatric Psychopharmacology Autism Network*

Abstract

Objective—Many children with Pervasive Developmental Disorders (PDDs) have serious, functionally-impairing behavioral problems. We tested whether Combined Treatment (COMB) with risperidone and parent training (PT) in behavior management is superior to Medication alone (MED) in improving severe behavioral problems in children with PDDs.

Method—This 24-week, three-site, randomized, parallel-groups clinical trial enrolled 124 children, aged 4 through 13 years, with PDDs, accompanied by frequent tantrums, self injury, and aggression. Children were randomized 3:2 to COMB (n= 75) or MED (n= 49). Participants received risperidone monotherapy from 0.5 to 3.5 mg/day (with switch to aripiprazole if risperidone was ineffective). Parents in COMB group (N=75; 60.5%) received a mean of 10.9 PT sessions. The primary measure of compliance was the Home Situations Questionnaire (HSQ) score.

Results—*Primary:* Intent-to-treat random effects regression showed that COMB was superior to MED on HSQ (p=.006) [effect size at Week 24 (d)= 0.34]. The HSQ score declined from 4.31 (±1.67) to 1.23 (±1.36) for COMB compared with 4.16 (±1.47) to 1.68 (±1.36) for MED. *Secondary:* Groups did not differ on Clinical Global Impressions–Improvement scores at end-point; compared with MED, COMB showed significant reductions on Aberrant Behavior Checklist Irritability (d=0.48; p= .01), Stereotypic Behavior (d=0.23; p= .04), and Hyperactivity/

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Noncompliance subscales (*d=0*.55; *p*= .04). Final risperidone mean dose for MED was 2.26 mg/day (0.071 mg/kg), compared to 1.98 mg/day for COMB (0.066 mg/kg) (*p*=.04).

Conclusion—Medication plus PT resulted in greater reduction of serious maladaptive behavior than medication alone in children with PDDs, with a lower risperidone dose.

INTRODUCTION

Autistic disorder (autism) is a neurodevelopmental disorder characterized by qualitative impairments in social interaction and communication, repetitive behavior, and a restrictive range of interests.[1] Autistic disorder, pervasive developmental disorder not otherwise specified (PDD—NOS), and Asperger's disorder are currently classified as pervasive developmental disorders (PDDs). The PDDs are often associated with additional problems including overactivity, impulsiveness, tantrums, aggression, and self-injury that interfere with daily living.[2–4] These behaviors are impairing in their own right, but they can also place considerable strain on families (parents and siblings), teachers, and other caregivers. Children with PDDs characteristically have adaptive behavior scores substantially below what would be expected from their mental ages.[5] This gap between adaptive behavior and mental age may be a consequence of syndromal traits and maladaptive behaviors.

Pharmacotherapy is common among individuals with PDDs, with community-based surveys suggesting a prevalence of about 45%[6,7] and up to 83% over the past year.[8] Commonly-used agents include selective serotonin reuptake inhibitors, antipsychotics, alpha 2 adrenergic agonists, psychostimulants, and anticonvulsants. Empirical support for use of these agents in children with PDDs varies widely. In 2002, the NIMH Research Units on Pediatric Psychopharmacology (RUPP) Autism Network reported that risperidone reduced serious behavioral problems (e.g., tantrums, aggression, self injury) in 101 children with autism.[9] Another acute study by Shea et al.[10] showed similar symptom reduction with risperidone. A subsequent report by the RUPP Autism Network indicated a high relapse rate when risperidone was replaced with placebo after six months of treatment as compared with risperidone maintenance.[11] In October, 2006, the FDA approved risperidone for children with autism accompanied by irritability (including tantrums, aggression, and self injury) (http://www.fda.gov/bbs/topics/news/2006/new01485.html).

Despite efficacy of risperidone for treating problem behavior in children with autism,[9, 10] this medication does not improve core symptoms of autism, or produce marked effects on learning or adaptive behavior. Most patients relapse upon discontinuation.[11] Furthermore, risperidone and other atypical antipsychotics are associated with adverse events (AEs) such as weight gain, which can increase the risk for health problems associated with obesity. Thus, practitioners face major clinical dilemmas. Therefore, we designed a trial to test the usefulness of a behavioral intervention in combination with risperidone to reduce maladaptive behavior and improve adaptive behavior.[12]

Our review of the PDD literature suggested that **parent training (PT)** based on principles of applied behavior analysis (ABA) had the most empirical support. Most successful programs for children with PDDs include a PT component that is based, at least in part, on ABA principles (e.g., the LEAP Program;[13] the Individualized Support Program;[14] the Pivotal Response Training Model;[15] and the Douglas Developmental Center Program[16]). PT uses parents as behavior change agents to promote skill acquisition and generalization of acquired skills to home and community. Common PT elements include teaching behavioral principles and management techniques, role playing, homework assignments followed by review and feedback, and gradual reduction in session frequency. Other elements include teaching play and social skills, use of visual communication techniques, home visits for consultation, telephone consultation, and gradual reduction in session frequency.[17]

Consultation with teachers is often used as well.[18] Training can be provided individually or in groups. Prior research has demonstrated that parents can learn techniques for reducing problem behaviors, increasing compliance, and improving adaptive skills.[19–25] To date, there have been only a few RCTs using PT for children with PDDs and fewer multisite trials.[26–33] We discussed these at length in a complementary paper.[18] Challenges of conducting multisite trials include the need for a treatment manual and therapist training to ensure treatment fidelity across sites. Therefore, in preparation for this study, we developed a PT curriculum and conducted a pilot trial to demonstrate that the intervention was acceptable to parents and could be uniformly applied across sites.[18, 34]

Hypotheses

Building upon our previous trial with risperidone, this study was designed to test whether risperidone plus PT would be superior to risperidone alone in children with PDDs and serious behavior problems. Three hypotheses are addressed in this paper. *Primary hypothesis:* Combined Treatment (COMB) will produce significantly greater compliance, compared with Medication-Only (MED), as assessed by the Home Situations Questionnaire (HSQ).[35] *Secondary:* COMB will be associated with higher likelihood of positive response than MED on the Improvement item of the Clinical Global Impressions (CGI) scale. *Exploratory:* COMB will produce significantly greater improvement in other maladaptive behavior domains measured by the Aberrant Behavior Checklist (ABC) and a clinician measure of repetitive behavior.

METHODS

Additional information regarding the background, feasibility, and methods for this study are described in detail elsewhere.[12,18,34] The institutional review boards of the clinical sites approved this investigation, and the parents or legal guardians of all child participants provided written informed consent.

Sample Characteristics

Key inclusion criteria were: (a) presence of PDD (autism, PDD-NOS, Asperger's disorder) established by DSM-IV-TR clinical criteria[1] and corroborated by the Autism Diagnostic Interview-Revised (ADI-R);[36] (b) age 4 to 13 years inclusive; (c) ≥ 18 on the Irritability subscale of the parent-rated ABC; [37,38] (d) CGI—Severity score ≥ 4; (e) medication free for two weeks for most psychotropic drugs, and for four weeks for fluoxetine and/or depot neuroleptics; (f) IQ ≥ 35 or mental age ≥ 18 months as assessed by Stanford Binet, Leiter International Performance Scale, or Mullen Scales of Development; and (g) if taking anticonvulsant, seizure-free for ≥ six months and with stable dose for four weeks. Exclusion criteria included (a) positive Beta HCG pregnancy test for girls; (b) prior adequate trial of risperidone; (c) other PDD (i.e., Rett's disorder, Childhood Disintegrative Disorder); (d) lifetime diagnosis of schizophrenia, other psychotic disorder, bipolar disorder, or current diagnosis of major depression, obsessive compulsive disorder, or substance abuse; (e) significant medical condition (e.g., heart, liver, renal, pulmonary disease), unstable seizure disorder, or significant abnormality on routine laboratory tests.[12]

Design

This 24-week, multi-site parallel-groups trial employed blinded evaluation with a planned 2:1 randomization to COMB and MED, respectively. The 2:1 randomization was adopted to enhance recruitment on the assumption that most families would prefer combined treatment. Due to chance, the actual ratio obtained was nearly 3:2. Each subject was followed by two clinicians: a *treating clinician* who monitored medication dose and AEs, but was otherwise blind through Week 8, and an *independent evaluator* who was blind to treatment assignment

throughout the whole study. Subjects randomized to COMB received PT from a behavior therapist trained on the RUPP manual.[12] Three parties knew the identity of families receiving PT: the families themselves, study coordinators, and site behavior therapists. After Week 8, the *treating clinician* was permitted to be unblinded if the subject's clinical situation necessitated team consultation.

Following informed consent, all participants were screened as follows: diagnostic assessment, medical evaluation (including ECG, medical history, routine laboratory tests), ADI-R interview, parent ratings on HSQ and ABC, and IQ testing. Subjects receiving ineffective medication were given a plan to taper their medication. The Baseline, which followed screening by four weeks or less, included parent ratings on the HSQ and ABC, and parent interviews with the Vineland Adaptive Behavior Scales.[39] Subjects who met entry criteria were randomized to MED or COMB. During the first 8 weeks, subjects were seen weekly to monitor medication response. Risperidone was adjusted according to the study schedule for 4 weeks, though the treating clinician could delay a planned increase or reduce dosage to manage AEs. There were no planned dose increases between Weeks 4 and 8, but clinically-indicated adjustments could be made by agreement of a cross-site clinical panel. At Week 8, subjects were assessed for their response to risperidone. Subjects who did not show a positive response to risperidone (defined below) could be switched to aripiprazole and continue in the study. PT also began at Baseline and continued for a planned minimum of 14 sessions over 16 weeks. PT sessions were scheduled with follow-up medication visits or at another convenient time for the family. The majority of PT concluded at Week 16, followed by a face-to face "Booster" session and two follow-up telephone consultations (conducted at 2-week intervals) to maintain treatment gains. Week 24 was the last visit in the randomized trial.

Study Instruments

ADI—R—The ADI—R[36] is a semi-structured interview, typically taking about three hours, that assesses reciprocal social interaction, communication, and restricted and repetitive behavior. Thus the ADI surveys domains relevant to PDDs and helped support the PDD diagnosis.

HSQ—The HSQ[35] is a 20-item parent-rated scale that captures noncompliant behavior in everyday circumstances (e.g., getting dressed for school; when caregiver is occupied on the telephone) over the previous 2 weeks. Questions answered affirmatively (i.e., noncompliance) are then scored on a 1–9 Likert scale (ranging from mild to very severe). We added 5 items to make the instrument more pertinent to children with PDDs (e.g., "When there is an unexpected change in daily routine"). The HSQ score was calculated by adding values from those rated on the Likert scale and dividing by 25. Because our PT package focused on reducing noncompliance to promote daily living skills, the HSQ was the primary outcome measure. To assess internal consistency of the 25-item HSQ, we computed coefficient alpha[39] for the Baseline ratings. Alpha was 0.92, suggesting excellent internal consistency.

Vineland Adaptive Behavior Scales (VABS)—The VABS is a parent interview designed to assess functional skills in three adaptive domains: Communication, Socialization, and Daily Living Skills.[40] The VABS also provides an Adaptive Composite Score, which is an estimate of global adaptive behavior. Findings for adaptive behavior and several related outcomes are reported in a subsequent paper.

CGI—We used the standard CGI—S to establish *severity* of the disorder and the CGI—I to measure *improvement*. Raters were trained to reliability using methods employed in our previous autism trials.[41]

ABC—The ABC is a 58-item rating scale that is completed by a caregiver, usually a parent or a teacher.[37] Its subscales are (a) Irritability (15 items), (b) Lethargy/Social Withdrawal (16 items), (c) Stereotypic Behavior (7 items), (d) Hyperactivity/Noncompliance (16 items), and (e) Inappropriate Speech (4 items). The ABC was empirically derived to assess treatment effects, and it has sound psychometric characteristics.[38] Parents were asked to consider the child's behavior over the last four weeks at Screen and Baseline or since the previous visit during other study phases. We employed the ABC Irritability subscale to confirm eligibility (presence of tantrums, aggression, self injury), to assess treatment response at Week 8 (to determine if risperidone treatment should continue), and as an exploratory measure to assess additive effects due to PT.

Children's Yale-Brown Obsessive Compulsive Scale—PDD Version (CY-BOCS—PDD).[42]—The CY-BOCS-PDD is a clinician-rated interview designed to evaluate repetitive behavior in children with PDDs. It is a modification of the CY-BOCS, developed to assess typically-developing children with obsessive compulsive behavior. Because of language limitations in children with PDDs the CY-BOCS—PDD only includes the five compulsion items: Time Spent, Interference, Distress, Resistance of repetitive behavior, and Control of repetitive behavior. Each item is rated from 0 (none) through 4 (extreme), and scores can range from 0 to 20.

Definition of Positive Drug Response—As in the original RUPP risperidone trial, a positive clinical response was determined by a rating of 1 or 2 (Very much/Much improved) on the CGI—I *and* by a reduction of ≥25% on the ABC Irritability subscale. If the participant did not meet this criterion by Week 8, risperidone was phased out and replaced with aripiprazole. If a participant did not have a positive response to either, we encouraged parents in PT to continue attending training sessions and scheduled assessments. For families who were unable or unwilling to attend remaining sessions, we attempted to obtain all end-point measures at that time. Aripiprazole is a partial dopamine agonist, which differentiates it from risperidone and other atypical antipsychotics. This suggested that it might be effective in cases for whom risperidone was not. Finally, preliminary data indicated that aripiprazole has a low risk of motor side effects, weight gain, and hyperprolactinemia,[12] which appeared to make it an ideal "back-up" medication.

PT and Fidelity Procedures

PT was delivered by one therapist per parent or couple. Sites employed a behavioral team comprising two doctorally-prepared or masters-level clinicians plus research assistant. Therapeutic teams used a structured treatment manual outlining the tasks for each session, including a therapist script, needed materials (e.g., instructive videotapes, activity sheets, homework tasks for families), and data collection forms. Prior to starting the trial, therapists were certified by PT supervisors. Certification was based upon supervisors' reviewing and rating a set of 11 tapes of parent sessions, and the establishment of 80% treatment fidelity. Rogers and Vismara[43] characterized such use of manual and procedures for ensuring reliable treatment, as meeting the highest standard of PDD treatment.

The therapists contacted subjects' schools to obtain details on any behavioral programs there. However, heterogeneity in school placements and supports obviated active collaboration between therapists and school personnel. The PT package consisted of 11 core treatment sessions, 3 optional, and up to 3 booster (2 via phone; 1 in person) sessions

(maximum of 17 sessions), each 60–90 minutes, delivered individually to families. The optional sessions could be drawn from 6 possible topics (e.g., toileting, sleep, time-out). Families attended 7–9 weekly sessions, and the remainder of the sessions were delivered on a flexible schedule, about every other week, through Week 24. Instruction included use of preventive approaches such as use of visual schedules, effective use of positive reinforcement, teaching compliance, teaching functional communication skills, and teaching specific adaptive skills. Sessions employed combinations of direct instruction, use of video vignettes, practice activities, behavior rehearsal with feedback, and role-playing. Each family was given individualized homework assignments between sessions, and parents were taught to collect data on children's behavior. Training was further individualized by selecting optional sessions and assignments based upon each child's functioning level (e.g., younger children with an intellectual disability might work on toilet training, while families with older children with Asperger's disorder might focus on token economy systems). Behavior therapists conducted initial and follow-up home visits to assess parental acquisition of behavioral interventions and made two follow-up phone calls to answer questions and offer additional support.

Once certified, therapists continued to rate all of their own sessions for treatment fidelity. All PT sessions were video taped, and 10% were randomly selected and reviewed for ongoing fidelity throughout the study. Therapists also rated parent participation via the Parent Treatment Adherence scale. This tracked parents' completion of homework assignments from the prior visit and parents' ability to participate in exercises and demonstrate understanding of training materials. Assignments attempted and barriers encountered were also discussed.

Dosing of Risperidone and Aripiprazole—Risperidone dosing over the first four weeks was guided by a schedule based on the child's weight. Children weighing 14 to 20 kg started on 0.25 mg/day with gradual increases to a maximum of 1.75 mg. For youngsters weighing 20 to 45 kg, dosing started at 0.5 mg/day and graduated to a maximum of 2.5 mg/day; for children weighing > 45 kg, dosing started at 0.5 mg/day with gradual increases to a maximum of 3.5 mg. Clinicians were allowed to decrease dosage or delay a scheduled increase to manage AEs. If response to risperidone was unsatisfactory, treatment was switched to aripiprazole, which was increased as risperidone was tapered.[12]

Statistical Procedures

Baseline characteristics were compared using *t*-tests for continuous variables, chi-squares for nominal variables, and Mantel-Haenszel tests for ordinal variables. Efficacy analyses used the intent-to-treat principle, and all 124 randomized subjects were included. Two subjects (both in COMB) did not have a post-randomization assessment; for them, the baseline observation was carried forward to the 2-week time point for the random regression modeling. Random effects regression, incorporating all available data, was used to compare rates of change in continuous outcome variables by treatment group over time.[44] Under the assumption that missing data are missing at random (i.e., missing values may be dependent on observed but not unobserved data), random regression models are more robust to missing data than most alternatives.[45] Given that prior outcome assessments describe the trajectory of individual change in subjects who drop out relative to subjects who do not, estimates of treatment effects will be unbiased. The assumption is supported by frequent assessment of outcome throughout the trial. Given fewer assumptions about missing data, random regression models are more robust to missing data than most alternatives.

The regression models included fixed effects for treatment (2 levels), time (continuous), site (3-levels) and their interactions. There were no significant site-by-treatment or site-by-

treatment-by-time interactions for any outcome; therefore, site was omitted from the models. Covariate adjustment was also included for baseline values. Trajectories of change were allowed to vary across individuals by including random effects for the intercept and slope terms that were also permitted to covary. To accommodate the possibility for non-linear relationship of the efficacy variables with time due to the early precipitous decline, quadratic and cubic functions of time were examined. Interactions of the quadratic and cubic functions with treatment group were not significant ($p>0.20$) and were therefore excluded from the models. Two-sided *p*-values are presented for the treatment-by-time interaction, which compared the slopes of change in outcome following randomization. Comparison of treatment effects by IQ subgroups (<70 vs ≥ 70) was performed by examining the interaction of treatment and the treatment-by-time effects with IQ subgroup.

To simplify interpretation, primary and secondary outcome measures are presented as least squares (LS) means and standard deviations at each timepoint estimated using the mixed model approach described by Carpenter and Kenward[46]. Effect sizes (Cohen's *d*)[47] were estimated by taking the difference between treatment groups of unadjusted mean changes from Baseline to Week 24 (or alternative timepoints) divided by the pooled baseline standard deviation. The proportion of positive responses on the CGI-I were compared across time using Generalized Estimating Equations (GEE) to account for correlation arising from repeated measures.[48] Comparisons of adverse event rates were made using Chi-squares or Fisher's Exact tests. Analyses were performed using SAS Version 9.1.

RESULTS

Subject Characteristics

As shown in Figure 1, 199 potential participants were screened, and 124 (62%) were randomized to this trial. Of the 48 ineligible to participate, 18 (38%) did not have a PDD, 14 (29%) had ABC Irritability scores less than 18 (2 children failed both criteria), and 5 (10%) had other DSM diagnoses that were exclusionary. The remaining screen failures were excluded for a multitude of reasons (across 5 inclusion/exclusion criteria) or because of a threat to the protocol (e.g., already receiving significant behavior therapy). Of those randomized, 49 (39.5%) received MED and 75 (60.5%) received COMB. There were 105 boys (85% of sample) and 19 girls (15%). The two groups were similar with respect to household income, parental education, and educational placement (see Table 1). Most clinical characteristics, including the HSQ, were similar across treatment groups. However, ABC Stereotypic Behavior, Vineland scores, IQ, and use of anticonvulsant medication were different across treatment groups. The MED group had lower functional skills and was more likely to be treated with anticonvulsants.

Treatment Fidelity and Exposure To Treatments

Mean treatment fidelity ranged from 45% to 100%, with a mean of 95.34% (SD=9.48%). The sessions with lower levels of fidelity were the result of pressing clinical issues requiring departure from the manual. The median and mode for treatment fidelity were both 100%, indicating very high overall levels.

Table 2 contains information on exposure to study treatments for Weeks 8, 16, and 24. This is presented separately for MED, COMB, and for PT sessions. As assessed by *t*-tests, doses were not significantly different at Weeks 8 and 16. By Week 24, however, dosage of risperidone was higher in the MED group (2.26 mg/day; 0.071 mg/kg) than in the COMB group (1.98 mg/day; 0.066 mg/kg) ($p=0.04$, two-sided test).

Primary and Secondary Outcome Measures

Figure 2 shows the results for our primary outcome, HSQ Severity score. After 24 weeks of treatment, the HSQ score declined 71% (from 4.31±1.67 to 1.23±1.36) for COMB compared with 60% (4.16 ± 1.47 to 1.68 ± 1.36) for MED. This difference in the rate of change in HSQ across treatment groups was significant (p= .006 treatment by time interaction from random effects regression) with a standardized effect size at week 24 of 0.34. The GEE model for CGI-I difference between treatment groups was not significant (P=0.74).

The LS means for all continuous variables are presented in Table 3. In addition to HSQ mean score, the ABC Irritability, Stereotypic Behavior, and Hyperactivity/Noncompliance subscales showed significant group differences, with COMB faring better over time. Effect sizes were computed for the differences between COMB and MED groups. Effect sizes were small (d < 0.20) to Week 16; however, at Week 24, the effect sizes were in the medium range (favoring COMB) for ABC Irritability (d=0.48) and Hyperactivity/Noncompliance (d=0.55), but small for Stereotypic Behavior (d=0.23).

Because the groups differed on IQ at baseline, we evaluated the possible influence of IQ on treatment effect. There was no interaction of treatment and treatment-by-time effects with IQ. We also looked at the 53 participants with IQs below 70 and the 69 with IQs 70 and above. The effect of treatment did not differ in these subgroups.

Weight, Height, and Body Mass Index (BMI)

Changes in weight, height, and BMI from Baseline to the last observed visit are shown in Table 4. Both groups had significant gains in height and substantial gains in weight and BMI. As compared by ANCOVA, the differences between groups were not significant in weight, height, or BMI on percentile-normed growth lines.

Adverse Events

The AEs that occurred during the trial for 5% of subjects or more appear in Table 5. Rhinitis was the most common AE (n= 99; 79.8%); ear infection (n=8; 6.5%) was least common. In general, the frequency of AEs was no different across groups, although insomnia (49.0% and 30.7%, respectively) and epistaxis (14% vs 4%, respectively) were reported more often for MED (p= .04 & .05, respectively, two-sided). Four serious AEs (SAEs) requiring hospitalization were reported in the MED group: Adenoidal hypertrophy, ostotomy, viral infection, and tonsillectomy. None was attributed to treatment. One additional SAE (hospitalization for seizures) was reported for a child during screening (who did not continue in the study). Fourteen severe AEs (one was also counted as one of the 5 SAEs) were reported for 10 participants: Dystonia, dyskinesia, and dysarthria (one subject); convulsions; pyrexia and vomiting (one subject) were reported for MED; convulsions; fatigue; sedation; adenotonsillectomy; tonsillectomy; fatigue; rash; headache were reported for COMB.

DISCUSSION

To our knowledge, this is the first RCT to examine the combination of parent training and medication in children with PDDs. The primary outcome variable, HSQ score, showed additive benefit (p=.006) with COMB, with a between-groups effect size of 0.34 at Week 24. This added effect of PT was detectable over and above the large treatment effect of medication alone. COMB also showed added benefit in reducing the serious behavioral problems that brought the children into the trial, with an effect size of 0.48 for ABC Irritability (p=.01) and an effect size of 0.55 for ABC Hyperactivity/Noncompliance (p= .04). Finally, these improvements due to PT were achieved with a 14% lower dose of risperidone in COMB than MED (p= .04).

The impact of risperidone in this study was somewhat larger than the effect observed in our original RUPP Autism Network trial.[9] In that study, the within-group effect size for subjects randomized to risperidone was 1.9 at Week 8, whereas effect size for the MED group in the current trial was 2.3. In the first RUPP trial, the positive response rate was 70% at Week 8. By contrast, in this study only 12 subjects of the entire sample (9.7%) did **not** meet threshold for positive response and thus crossed over to aripiprazole. The larger effect size in this trial may be partially explained by the absence of placebo control.

Our findings appear similar to, although more striking than, results from the Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (ADHD) (MTA study). Although the primary MTA analyses failed to find a significant difference between COMB and MED alone on individual outcome variables,[49] Swanson et al.[50] found an effect size of 0.26, in favor of COMB treatment, on a composite index that included both ADHD and Oppositional Defiant Disorder symptoms. In the current study, a measure of noncompliance (HSQ), explosive behavior (ABC Irritability), and hyperactivity (ABC Hyperactivity) were all significant with larger effect sizes than that reported in the MTA. As in the MTA trial, the COMB group in our study achieved gains with significantly lower medication doses. In both studies, the beneficial effects of added behavioral treatment appeared to increase over time.[51] Other important differences are that the behavioral intervention in the MTA was more intensive and delivered over a greater period of time than the PT program in our study. Thus, the behavioral treatment tested here produced additive benefit at lower cost than the MTA study, albeit for a different population and target symptoms.

It seems that a logical next step will be to conduct effectiveness studies with the PT manual and supporting materials that we developed. Among other things, it will be important to determine if efficacy is maintained and whether parents will persist with the 9–12 recommended core sessions.

Adverse Events

With the exception of insomnia and epistaxis, which were more common in the MED group, the profile of AEs was similar across treatment groups. Many of the reported AEs are common complaints of childhood that would be expected to occur over 6 months. It is interesting to compare the AEs documented here with those in our earlier study,[9] although the earlier trial lasted only 8 weeks. The following AEs were also reported, in this order of frequency, in our original risperidone study, where risperidone separated from placebo at $p \leq .06$ two-sided: Appetite increase, fatigue, drowsiness, constipation, drooling, dizziness, tremor, tachycardia, and weight gain. The occurrence of seizures in two subjects is difficult to interpret, given the relatively high risk of seizures in children with PDDs. Nevertheless, these events suggest that surveillance of seizures is warranted in such children treated with antipsychotics. We also observed BMI percentile increases of approximately 15 and 19 points for MED and COMB, confirming substantial weight gains noted in other studies. In keeping with current guidelines, weight and metabolic indices should be monitored in children receiving risperidone or other atypical antipsychotics.

Limitations

One may argue that the trial should have included a PT-alone condition. It is possible that drug effects and PT effects were not additive in a straightforward manner and that the two treatments synergistically moderated each other. Such effects have been observed occasionally in clinical trials.[52] We did not include a PT-alone condition for several reasons. First, the effect size in the first risperidone trial on ABC Irritability was 1.2 for risperidone. We concluded that our 16-week PT program would not be sufficient in intensity to produce

such large effect sizes in this population. Thus, it would be questionable, ethically, to randomize subjects to an almost-certainly unequal treatment. Second, because our interest was to develop an exportable PT program, as an additive treatment for children with PDD and serious behavioral problems, we decided against an intensive behavioral intervention. If we developed an intensive behavioral program that could be compared directly with medication, even if it worked, it would not be exportable. A final consideration was time and cost. Enrollment of 124 subjects with serious behavior problems at three sites required 3 years. If we added a third group, the study would have taken at least another year and would have been substantially more expensive.

Another potential limitation is that subjects in COMB had more contact with therapists (10.9 sessions, on average). It is possible that therapist contact alone, rather than the PT, was responsible for the differences between groups. A third limitation was the lack of independent informant ratings, such as could be provided by teachers. Given the 6-month duration of the trial, and that participants were enrolled throughout the year, it would not be possible to gather ratings from the same teacher at Week 24 for subjects enrolling in spring and summer. Fourth, non-equivalence of the groups at baseline (with the MED group functioning at a lower level) complicated interpretation, although further statistical analysis ruled out any effect of IQ on the HSQ or ABC Irritability. Finally, the sample size was relatively small compared to many trials (although larger than the vast majority of trials in the PDD field). Finally, the HSQ used in this study was lengthened by five items to make it more relevant to PDDs, and the psychometric effect of adding these items is unknown.

Clinical and Public Health Implications

Although the current behavioral package called for 11 standard sessions and up to 6 optional sessions, the mean number actually delivered was 10.9 sessions. *Indeed, we selected PT for this trial because it is both practical and feasible*. As parents are the agents of change, PT is less expensive than many other forms of psychosocial intervention. Our results suggest that PT is an effective and potentially-affordable intervention for children with PDD and serious behavioral problems. The PT program is in manual format with therapist scripts, homework assignments, parent handouts, and other teaching materials. We plan to make the manual and accompanying materials available for broad use. The development of this potentially-exportable intervention for children with PDDs and serious behavioral problems is consistent with reports from expert panels[53] and a step toward dissemination of PT in this population. PT alone may be helpful in children with PDD and problem behaviors that are significant but below threshold for pharmacotherapy. The steady increase in the number of identified cases of PDD underscores the need for developing and disseminating effective behavioral interventions.

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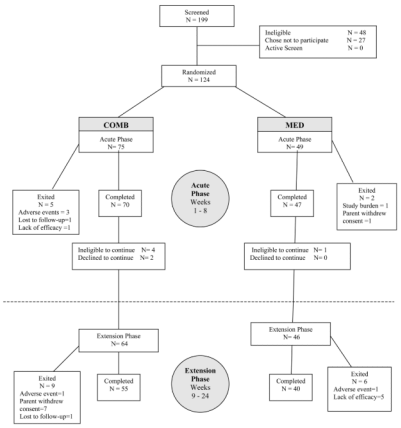

Figure 1.

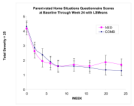

Figure 2.

Table 1

Baseline Demographic and Clinical Features of MED and COMB Groups (N=124)

Variable	MED (%/SD)	COMB (%/SD)	P-Value
Age			
Years	7.50 (2.80)	7.38 (2.21)	.86
Race and Ethnicity*			
White/Non-Hispanic	34 (69.4)	59 (78.7)	.15
Hispanic	7 (14.3)	4 (5.30)	
African American	7 (14.3)	9 (12.1)	
Asian American	0 (0.0)	3 (4.0)	
Native American	1 (2.0)	0 (0.0)	
Educational Placement**			
Full time, Regular Education	10 (20.4)	18 (24.0)	.44
F/T, Regular Education, with Aide	0 (0.0)	3 (4.0)	
Regular Ed, with Some Special Ed.	5 (10.2)	4 (5.3)	
Special Education Classroom	8 (10.3)	14 (18.7)	
Special Elementary School	3 (6.1)	2 (2.7)	
Home School	4 (8.2)	5 (6.7)	
Special Preschool	11 (22.4)	11 (14.7)	
Regular Preschool	6 (12.2)	8 (10.7)	
No School	2 (4.1)	12 (16.0)	
PDD Diagnosis			
Autistic Disorder	32 (65.3)	49 (65.3)	.83
PDD-NOS	13 (26.5)	22 (29.3)	
Asperger's Disorder	4 (8.2)	4 (5.3)	
Home Situations Questionnaire			
Average Severity Score	4.16 (1.47)	4.31 (1.67)	.61
"Yes" Count	18.9 (3.46)	18.6 (4.65)	.73
Clinical Global Imp. Severity			
Moderate (4)	14 (28.6)	25 (33.3)	.47
Marked (5)	19 (38.8)	33 (44.0)	
Severe (6)	15 (30.6)	17 (22.7)	
Extreme (7)	1 (2.0)	0 (0.0)	
Aberrant Behavior Checklist			
Irritability	29.7 (6.10)	29.3 (6.97)	.77
Social Withdrawal	17.1 (8.37)	15.2 (9.01)	.22
Stereotypic Behavior	10.6 (5.46)	7.59 (5.20)	.003
Hyperactivity/Noncompliance	36.1 (6.86)	35.3 (9.30)	.61
Inappropriate Speech	6.37 (4.03)	5.75 (3.43)	.36
Vineland Adaptive Behavior Scale			
Communication	53.2 (19.9)	61.1 (20.9)	.04
Daily Living Skills	41.1 (19.8)	50.8 (18.5)	.007

Variable	MED (%/SD)	COMB (%/SD)	P-Value
Socialization	53.5 (14.4)	59.5 (15.0)	.03
Composite	45.8 (15.5)	53.1 (15.7)	.01
IQ Category†			
Average	11 (22.5)	28 (38.4)	.02
Borderline	12 (24.5)	18 (24.7)	
Mild ID	9 (18.4)	14 (19.2)	
Moderate ID	17 (34.7)	13 (17.8)	
Anticonvulsant Medication	4 (8.2)	0 (0.0)	.02

Note. COMB= Medication plus parent training; Ed= Education; F/T= Full time; ID=Intellectual disability; MED= Medication alone.

*Participants classified themselves for ethnicity.

**No significant group difference as a function of educational placement.

†A subset of 78 subjects were also tested with the Stanford-Binet Intelligence Scale. For these participants, scores on the Stanford-Binet (mean 73.4; SD 19.4) was significantly lower than the Leiter Performance Scale (mean=79.3; SD=18.9) (P-value from the paired *t*-test was 0.0004). Leiter scores tend to be higher than most individually-administered IQ tests for children with impaired language; hence the IQ categories presented here may be somewhat "inflated."

Table 2

Group Exposure to Medication and Parent Training Treatments

Group and Treatment	Week 8	Week 16	Week 24
MED			
Dose			
Mean Mg per day	2.20	2.17	2.26
Mean mg/kg/day	0.072	0.068	0.071
Standard deviation	0.71	0.66	0.57
COMB			
Dose			
Mean Mg per day	2.02	1.98	1.98
Mean mg/kg/day	0.700	0.066	0.066*
Standard deviation	0.49	0.50	0.56
PT Sessions			
Number of sessions†	5.74	9.65	10.82
Standard deviation	1.76	2.84	3.16
OVERALL DOSE (all subjects)			
14–20 kg.	1.55	1.67	1.85
20–45 kg	2.17	2.11	2.12
>45 kg	2.97	2.79	2.46

Note. COMB= Medication plus parent training; MED= Medication alone. Of the 75 families assigned to Parent Training, 67 had an initial home visit and 50 had a follow-up home visit at Week 16. Forty-nine of the 75 families attended a face-to-face booster session. Fifty-five of the 75 children in COMB (73.3%) received all 11 core sessions.

† Sessions are presented cumulatively.

* p =.04.

Table 3

Least Squares Means and Standard Deviations[a] for Primary and Secondary Variables at Baseline and Weeks 8, 16, and 24.

		Baseline[b]		Week 8[c]		Week 16[d]		Week 24[e]		p*
		MED	COMB	MED	COMB	MED	COMB	MED	COMB	
HSQ Severity	M	4.16	4.31	1.59	1.60	1.61	1.48	1.68	1.23	.006
	S.D.	1.47	1.67	1.45	1.55	1.26	1.51	1.36	1.36	
ABC Irritability	M	29.69	29.33	12.52	11.95	13.60	12.10	14.53	10.96	.01
	S.D	6.10	6.97	8.69	8.21	9.34	8.05	9.90	6.64	
ABC Social Withdrawal	M	17.14	15.16	6.98	4.72	6.49	4.58	6.44	4.26	.78
	S.D.	8.37	9.01	7.63	6.31	7.56	6.07	7.16	5.17	
ABC Stereotypic†	M	10.55	7.59	5.23	2.89	5.73	3.34	6.25	3.20	.04
	S.D.	5.46	5.20	5.23	3.82	5.35	4.21	5.68	4.09	
ABC Hyperactivity	M	36.08	35.35	18.80	16.50	18.39	16.16	20.78	15.38	.04
	S.D.	6.86	9.30	10.99	10.69	10.62	10.87	12.38	10.23	
ABC Inappropriate Speech	M	6.37	5.75	3.34	2.54	3.35	2.43	3.30	2.56	.20
	S.D.	4.03	3.43	3.18	2.59	3.34	2.73	3.66	2.93	
CY-BOCS†	M	16.22	14.72	11.54	10.67	11.33	9.97	11.86	10.11	.62
	S.D.	2.47	2.85	3.92	3.26	4.48	3.98	4.47	3.83	

Note. ABC= Aberrant Behavior Checklist; CY-BOCS= Children's Yale-Brown Obsessive Compulsive Scale; HSQ= Home Situations Questionnaire.

[a] Least squares means and standard deviations were estimated using a mixed effect model with an unstructured covariance matrix as described by Carpenter and Kenward[46].

[*] *P*-value for the treatment by time interaction was derived from Random Regression analysis that allowed for a cubic relation of outcome with time. Sample sizes were as follows:

[b] 124;

[c] 101;

[d] 84;

[e] 75. We also analyzed by treatment and by diagnostic type (autistic vs. non-autistic), and diagnosis did not modify the treatment effect on the major variables of interest: Home Situations Questionnaire (*p*-value for interaction=0.76) and ABC-Irritability (*p*-value for interaction=0.91).

[†] Whereas the Stereotypic Behavior subscale from the Aberrant Behavior Checklist describes a variety of simple stereotypic behaviors, the Children's Yale-Brown Obsessive Compulsive Scale captures a much wider range of possible behaviors, including stereotypic behavior and more complex repetitive behavior.

Table 4

Changes in Weight, Height, and Body Mass Index Percentiles from Baseline to Last Observed Visit

Variable	Baseline		Last Observed Visit	
	Mean	(SD)	Mean	(SD)
Weight Percentile				
MED	69.27	(31.77)	81.15	(25.70)
COMB	67.55	(27.36)	80.98	(21.87)
Height Percentile				
MED	56.13	(32.53)	58.56	(30.73)
COMB	61.38	(31.04)	64.42	(29.48)
Body Mass Index				
MED	71.00	(30.57)	85.62	(21.28)
COMB	65.07	(27.87)	83.66	(18.69)

Note. COMB= Medication plus parent training; Med= Medication alone.

Table 5

Adverse Event Summary by Treatment Assignment (in Order of Overall Prevalence)

Adverse Event	MED (n=49)		COMB (n=75)		*p* Value
	N	(%)	n	(%)	
Rhinitis	39	(79.6)	60	(80.0)	.96
Cough	39	(79.6)	58	(77.3)	.77
Appetite increase	38	(77.6)	55	(73.3)	.60
Fatigue	33	(67.4)	60	(80.0	.11
Weight increase	40	(81.6)	53	(70.7)	.17
Somnolence	24	(49.0)	32	(42.7)	.49
Vomiting	19	(38.8)	34	(45.3)	.47
Excessive Saliva	16	(32.7)	36	(48.0)	.09
Enuresis	16	(32.7)	32	(42.7)	.26
Insomnia	24	(49.0)	23	(30.7)	.04
Headache	18	(36.7)	25	(33.3)	.70
Diarrhea	17	(34.7)	24	(32.0)	.76
Constipation	18	(36.7)	21	(28.0)	.31
Skin rash	12	(24.5)	24	(32.0)	.37
Anxiety	14	(28.6)	22	(29.3)	.93
Dyspepsia	9	(18.4)	21	(28.0)	.22
Polydipsia	11	(22.5)	17	(22.7)	.98
Nausea	12	(24.5)	15	(20.0)	.55
Pyrexia	8	(16.3)	18	(24.0)	.30
Dry mouth	14	(28.6)	11	(14.7)	.06
Pharyngitis	9	(18.4)	14	(8.7)	.97
Tachycardia	7	(14.3)	11	(14.7)	.95
Abdominal pain (upper)	6	(12.2)	11	(14.70)	.70
Dyskinesia	7	(14.3)	7	(9.3)	.39
Nasal congestion	7	(14.3)	6	(8.0)	.26
Tremor	4	(8.2)	9	(12.0)	.50
Dizziness	2	(4.1)	9	(12.0)	.20*

Adverse Event	MED (n=49)		COMB (n=75)		*p* Value
	N	(%)	n	(%)	
Epistaxis	7	(14.3)	3	(4.0)	.05*
Polyuria	3	(6.1)	7	(9.3)	.74*
Ear infection	2	(4.1)	6	(8.0)	.48*

Note. COMB= Medication plus parent training; Med= Medication alone. The data include all subjects assigned to risperidone (N=124), including 12 subjects who eventually switched to aripiprazole at some point.

*Fisher's exact test. All other comparisons were done by Chi Square tests.

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