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# A 1.5-Year Follow-Up of Parent Training and Atomoxetine for Attention-Deficit/Hyperactivity Disorder Symptoms and Noncompliant/Disruptive Behavior in Autism

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## Abstract

***Objective:*** To examine status of children with autism spectrum disorder (ASD) 10 months after a 34-week clinical trial of atomoxetine (ATX) and parent training (PT).

***Methods:*** In a 2×2 design, 128 children with ASD and attention-deficit/hyperactivity disorder (ADHD) were randomly assigned ATX, PT+placebo, PT+ATX, or placebo alone. PT was weekly for 10 weeks, and then monthly. ATX/placebo was titrated over 6 weeks [≤1.8 mg/kg/d], and then maintained until week 10. Responders continued to week 34 or nonresponse. Placebo nonresponders had a 10-week ATX open trial; ATX nonresponders were treated clinically. All continued to week 34. With no further treatment from the study, all were invited to follow-up (FU) at 1.5 years postbaseline; 94 (73%) participated. Changes from Week 34 to FU and from baseline to FU were tested by one-way analysis of variance or chi-squared test. PT versus no PT was tested by chi-squared test, Fisher's exact test, Welch's *t*-test, Student's *t*-test, and Mann–Whitney's U test.

***Results:*** For the whole sample, the primary outcomes (parent-rated ADHD on the Swanson, Nolan, and Pelham [SNAP] scale and noncompliance on the Home Situations Questionnaire [HSQ]) deteriorated mildly from week 34 to FU, but were still substantially better than baseline (SNAP: $t = 12.177$, $df = 93$, $p < 0.001$; HSQ: $t = 8.999$, $df = 93$, $p < 0.001$). On the SNAP, 61% improved ≥30% from baseline (67% did at week 34); on noncompliance, 56% improved ≥30% from baseline (77% did at week 34). Outcomes with PT were not significantly better than without PT (SNAP $p = 0.30$; HSQ $p = 0.27$). Originally assigned treatment groups did not differ significantly. Only 34% still took ATX; 27% were taking stimulants; and 25% took no medication.

***Conclusions:*** The majority retained their 34-week end-of-study improvement 10 months later, even though most participants stopped ATX. For some children, ATX continuation may not be necessary for continued benefit or other drugs may be necessary. Cautious individual clinical experimentation may be justified. Twelve sessions of PT made little long-term difference. ClinicalTrials.gov Identifier: Atomoxetine, Placebo and Parent Management Training in Autism (Strattera) (NCT00844753).

**Keywords:** atomoxetine, parent training, ADHD, follow-up studies, autism spectrum disorder

## Introduction

Hyperactivity and other symptoms of attention-deficit/hyperactivity disorder (ADHD) are common in autism spectrum disorder (ASD) (Lecavalier 2006; Simonoff et al. 2008). Unlike its predecessor, the *Diagnostic and Statistical Manual, 5th Edition* (American Psychiatric Association 2013) allows both diagnoses concomitantly in children who meet criteria for both disorders, sanctioning what had become widespread clinical practice. Because ADHD symptoms are so frequent in ASD, it is important to understand whether the evidence-based interventions used for ADHD without ASD are appropriate for children who have both disorders. It is also important to examine what happens over time once those treatments have been started, an area with scant literature.

The Child Hyperactivity and Autism Research Treatment Study (CHARTS) randomly assigned 128 children with ASD who also met categorical and dimensional criteria for ADHD to atomoxetine (ATX) alone, ATX+parent training (PT) in behavioral management,

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placebo+PT, or placebo alone. The 10-week double-blind initial phase (Handen et al. 2015; Tumuluru et al. 2017) was followed by an extension to week 34 (Smith et al. 2016). We expected that PT effects would take more time to emerge, but would be longer lasting than ATX effects because PT teaches skills for parents to continue managing their child's behavior (Handen et al. 2015).

The *double-blind initial phase* showed that ATX, ATX+PT, and placebo+PT each resulted in more improvement than placebo alone on parent-rated ADHD symptoms (effect sizes $d = 0.57–0.98$, with $p = 0.0005$, 0.0004, and 0.025, respectively). *The extension* to week 34 showed that 59% of 10-week responders to the initial treatment continued to show response 6 months later and 37% of placebo nonresponders responded to an open ATX trial. Thus, the children in the study were generally better at the end (after 34 weeks) than when starting. The question then arises about how well that improvement holds up over even more time.

This article reports outcomes 1.5 years after baseline (week 78), about 10 months after cessation of study-provided 34-week treatment. During the follow-up (FU) interval from weeks 34 to 78, no systematic treatment was provided by the study; all participants returned to the clinic or other community care from which they had been recruited. Hypotheses were that (1) most of the 34-week improvement from baseline would be sustained at FU; (2) the majority would continue their 34-week response status to FU, whether responder or nonresponder; and (3) those whose parents received PT might fare better than those without PT.

## Methods

We previously described the background of this study (Silverman et al. 2014). It was approved by the institutional review boards at all sites; parents/legal guardians signed informed permission and children assented if able.

### *Sample characteristics*

Participants were 5.0–14.11 years old with a minimum mental age (MA) of 24 months, based on either the *Stanford-Binet 5th Edition* (Roid 2003) or Mullen Scales of Early Learning (Mullen 1989). All met criteria for an ASD (Autistic Disorder, Asperger's Disorder, Pervasive Developmental Disorder Not Otherwise Specified), by the Autism Diagnostic Interview-Revised (Rutter et al. 2003), and expert clinical evaluation using a DSM-IV-TR Interview (American Psychiatric Association 2000). They exhibited marked symptoms of overactivity and/or inattention at both home and school, based upon a mean item score ≥1.50 on the parent- and teacher-completed Swanson, Nolan, and Pelham (SNAP) scales (Bussing et al. 2008) and a Clinical Global Impression (CGI)-Severity score ≥4 (Guy 1976).

Participants were free of psychotropic medications (with the exception of stable doses of melatonin for sleep) for 2 weeks before randomization. A single anticonvulsant for seizure control was allowed, provided that stable doses and seizure-free status had been maintained for 6 months (one child took this). Children with serious medical conditions, major abnormalities on routine laboratory tests and electrocardiogram, prior adequate trial of ATX, or prior involvement in a highly structured PT program were excluded.

### *Design*

The initial 10-week double-blind phase was a randomized, parallel-group trial at three sites (University of Pittsburgh Medical Center, Ohio State University, and University of Rochester). Randomization was stratified by site in equal numbers to ATX, ATX+PT, placebo+PT, or placebo alone and balanced by MA (<6 years vs. ≥6 years). Families assigned to PT met with a behavior therapist trained to use the PT manual with fidelity. The second phase was an extension to week 34 (Smith et al. 2016). Those assigned to PT continued in PT during the extension. Responders continued blinded and nonresponders were treated openly. All were assessed at 34 weeks, the end of the extension. All were invited to the FU 1.5 years after baseline.

### *ATX dosage*

During the 10-week double-blind trial and in the subsequent open trial for placebo nonresponders, ATX doses were individually adjusted the first 6 weeks according to a weight-based dosage schedule, with medical clinicians allowed to delay increases or reduce doses due to adverse events (AEs). The daily dose was split into twice-daily administration. The initial dose was 0.3 mg/kg/d (rounded to nearest 5 mg) with weekly escalations by 0.3 mg/kg/d, unless there were limiting side effects or no further room for improvement, to a target dose of 1.2 mg/kg/d, and could be increased to a maximum of 1.8 mg/kg/d based on clinical response. This optimal dose was maintained during weeks 7–10.

### *Procedure*

At week 10, participants were rated as ADHD responders based on a CGI-Improvement rating of 1 or 2 for ADHD symptoms by blinded evaluators *and* a ≥30% decrease on the parent SNAP-IV. At the same time, participants were rated as noncompliance responders based on a CGI-Improvement rating of 1 or 2 for noncompliance by blinded evaluators *and* a ≥30% decrease on the Home Situations Questionnaire (HSQ) (Handen et al. 2015). Responders (either ADHD or noncompliance) remained in their assigned treatments without breaking the blind. Nonresponders had their medication blinding broken at week 10. Those who had received placebo began an open trial of ATX; those who had taken ATX were treated clinically (Handen et al. 2015). All continued in a study extension to week 34. The current data were collected 10 months later, 1.5 years after baseline.

At entry to the study, parents knew this FU was part of the research plan. To collect the FU data, research coordinators telephoned the parents and interviewed them regarding participants' school placements, intervening medical issues, current medications, hospitalizations, and general behavioral profile. Then, parents were offered the option of completing behavior rating forms, while on the phone call or later with mailed forms.

### *Measures*

**The CGI scale.** This includes subscales for severity and improvement (Guy 1976). The severity scale is scored from 1 (normal) to 7 (extremely ill), with a rating >4 (moderate) required for inclusion. The improvement score ranged from 1 (very much improved), through 4 (no change), to 7 (very much worse). The CGI was completed by blinded raters. Separate CGI ratings were obtained for ADHD and noncompliance.

**The SNAP-IV.** The SNAP-IV rating scale was used to measure ADHD and oppositional defiant disorder (ODD) symptoms (Bussing et al. 2008). The SNAP-IV ADHD, and ODD sections include the 18 DSM-IV symptoms of ADHD (9 inattention and 9 hyperactive/impulsive items) and 8 symptoms of ODD rated on a 0–3 scale. A mean item score of ≥1.5 on the parent *and* teacher

SNAP-IV 18 ADHD symptoms *or* the 9-symptom hyperactive-impulsive items, *or* the 9-symptom inattentive items served as study inclusion criteria. The teacher rating was used only for inclusion, not outcome.

Home Situations Questionnaire (HSQ). The HSQ was completed by parents to assess noncompliance (Barkley and Edelbrock 1987; Altepeter and Breen 1989; Barkley et al. 1999; Chowdhury et al. 2010). The 25-item HSQ was adapted by the Research Units in Pediatric Psychopharmacology (RUPP) Autism Network from the original to evaluate behavioral noncompliance in children with ASD (Chowdhury et al. 2010). Items are rated on 10-point Likert scales, ranging from 0 to 9.

Aberrant Behavior Checklist. The Aberrant Behavior Checklist (ABC) is a 58-item behavior checklist completed by parents. Items are scored on a 4-point Likert scale (from ''not a problem'' to ''severe''). Five subscales are derived: (1) irritability (15 items), (2) social withdrawal (16 items), (3) stereotypic behavior (7 items), (4) hyperactivity/noncompliance (16 items), and (5) inappropriate speech (4 items). The ABC is reliable, valid, and sensitive to treatment effects (Aman et al. 1985; Aman 2012).

### *PT and fidelity procedures*

Families assigned to PT met for individual sessions with a PT clinician weekly during the first 10 weeks, and monthly until the end of study treatment at week 34. Sessions were adapted from the RUPP Parent Training Manual and covered topics such as preventing behavior problems, reinforcement, time out, and planned ignoring (Silverman et al. 2014). Each session lasted 60–90 minutes and included didactic materials, videos, and role playing (Handen et al. 2015). Parents were given weekly homework assignments and kept data on target behaviors. Before the study, PT clinicians were certified by supervisors based on 80% or greater fidelity scores for implementation and scoring of manualized sessions with pilot families. Twice-monthly telephone conferences were held between site PT clinicians and supervisors to achieve standardization and provide feedback from randomly viewed tapes (Handen et al. 2015).

### *Statistical procedures for the FU*

Data analyses were completed with the intention-to-treat principle, with missing data points for questionnaire measures filled by using last-observation-carried-forward (LOCF) to week 34 or missing data at week 34. For comparisons at week 78 of parent treatment groups (ATX+PT and placebo+PT vs. ATX alone and placebo alone), categorical variables were analyzed through chi-squared or Fisher's exact tests, while continuous variables were analyzed with Welch's or Student's *t*-test for normalized distributions and Mann–Whitney's U test for distributions that could not be normalized. Comparisons among the four treatment groups at week 78 used an analysis of variance on continuous variables or chi-squared test for categorical variables. Sensitivity analyses were completed by comparing results using LOCF to results without LOCF. Further sensitivity analyses for continuous variables compared the primary results with the results of data transformed for normality. Sensitivity analysis did not show a difference from the primary analysis and will not be further mentioned.

During the blinded phase, responder status was determined by a combination of CGI-Improvement scores and ≥30% reduction in SNAP or HSQ for attention and compliance responders, respectively. However, CGI scores were not collected at the FU; for these analyses, attention responder status was defined as a ≥30% decrease from baseline in SNAP score, compliance responder status as a ≥30% decrease in HSQ, and combined (dual) responder status as being a responder for both attention and compliance. Responder statuses at week 78 were compared through chi-squared tests among the four originally assigned treatments, and between the two pooled groups that received PT and the two pooled groups that did not, and by whether a subject initially received an active treatment (ATX, ATX+PT, and PT+placebo) or placebo alone. For those who received PT, a multiple linear regression tested the effect of behavioral skill use and time on week 78 SNAP and HSQ scores.

Baseline demographics of subjects who completed the FU were compared to those who did not by chi-squared and Student's *t*-test. Demographic information and primary analysis were compared between subjects whose parents received PT and those who did not. In these exploratory analyses, statistical significance was set at $p < 0.05$, two-tailed, for all measures. All analyses were completed with SPSS 24 (SPSS, Inc., Armonk, NY).

## Results

Table 1 compares baseline demographic and clinical characteristics of those who returned for FU and those who did not. There was a sex difference, with significantly more retention of girls at FU. However, sex did not make a significant difference on FU outcome when checked in several different ways. Those participating in FU

Table 1. Baseline Comparison of the 94 Participants Available at 1-Year Follow-Up to the 34 Who Did Not Return for Follow-Up Assessment

| | *FU* (n = *94*) | *No FU* (n = *34*) |
|---|---|---|
| Diagnosis, *n* (%) | | |
| Asperger's disorder | 15 (16) | 6 (17.6) |
| Autistic disorder | 41 (43.6) | 16 (47.1) |
| PDD-NOS | 38 (40.4) | 12 (35.3) |
| Child race, *n* (%) | | |
| White | 75 (79.8) | 30 (88.2) |
| Black | 10 (10.6) | 0 (0) |
| Asian | 1 (1.1) | 0 (0) |
| Multiracial | 7 (7.4) | 3 (8.8) |
| Other | 1 (1.1) | 1 (2.9) |
| Other demographics | | |
| IQ from baseline, mean (SD) | 82.23 (23.5) | 80.1 (26.6) |
| Male, *n* (%) | 76 (80.9)* | 33 (97.1)* |
| Annual household income ≤60k, *n* (%) | 42 (44.7) | 18 (52.9) |
| Special education, *n* (%) | 56 (59.6)* | 13 (38.2)* |
| ADHD CGI-S, *n* (%) | | |
| Moderate | 25 (26.6) | 9 (27.3) |
| Marked | 48 (51.1) | 16 (48.5) |
| Severe | 21 (22.3) | 8 (24.2) |
| Noncompliance CGI-S, *n* (%) | | |
| Mild | 4 (4.3) | 1 (3.0) |
| Moderate | 46 (48.9) | 21 (63.6) |
| Marked/severe | 44 (46.8) | 11 (33.3) |

One participant's data not obtained from no-FU group for ADHD CGI-S and noncompliance CGI-S. For CGI-S, mild was defined as a score of 3, moderate as 4, marked as 5, and severe as 6.

*$p \leq 0.05$.

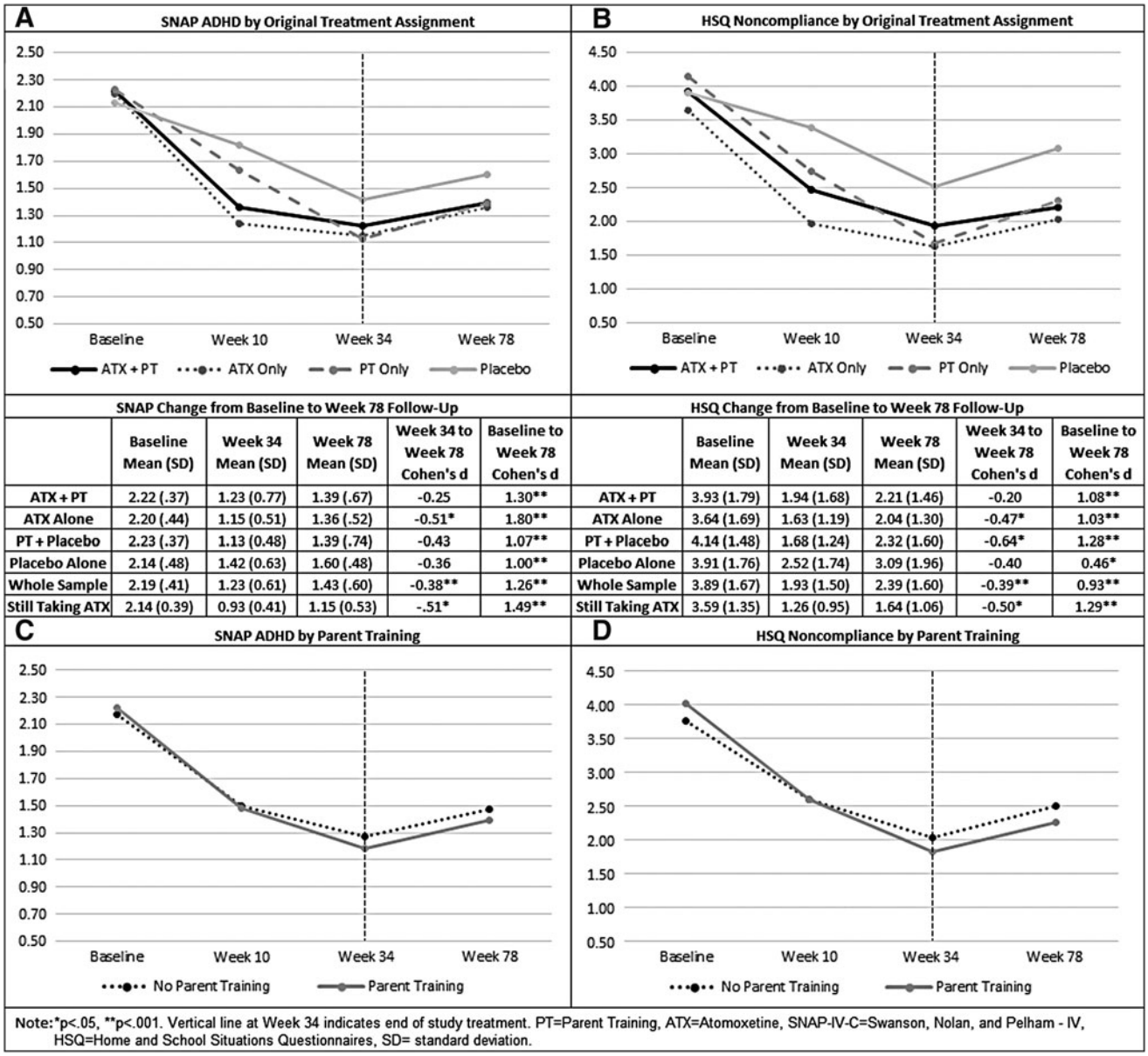
ADHD, attention-deficit/hyperactivity disorder; CGI-S, Clinical Global Impression-Severity; FU, follow-up; IQ, intelligence quotient; PDD-NOS, Pervasive Developmental Disorder-Not Otherwise Specified; SD, standard deviation.

attended special education classes significantly more often than those lost to FU.

Figure 1 shows the primary outcomes at the 4 pivotal times: baseline before treatment, week 10 at the end of the double-blind treatment, week 34 at the end of study-provided treatment, and week 78 at FU, by originally assigned treatment (Figure 1A,B) and by PT versus no PT (Figure 1C,D). Figure 1A and C show the SNAP ADHD mean over time, and Figure 1B and D show HSQ noncompliance over time. Regardless of originally assigned treatment, all had significant improvement with large effect sizes (Cohen's $d$ 1.0–1.8, $p < 0.001$) from baseline to 1.5-year FU, even after mild deterioration ($d$ 0.25–0.51, $p < 0.05$) following week 34 end-of-study-treatment.

Those originally assigned to placebo showed significantly less improvement from baseline to FU than those assigned to active treatment in both the HSQ ($t = -2.309$, $df = 92$, $p = 0.023$) and SNAP measures ($t = -2.039$, $df = 92$, $p = 0.044$). The slight advantage of PT over no PT over the same length of time was not significant for either SNAP ADHD ($t = 1.034$, $df = 92$, $p = 0.30$) or HSQ noncompliance ($U = 957$, $p = 0.27$).

Table 2 shows the FU medication by originally assigned treatment group and by PT versus no PT. One-fourth (24.7%) were taking no medication at FU and only one-third were still taking ATX; 27% were taking a stimulant, 13% an alpha-2 agonist, and 10% an antipsychotic. No differences between originally assigned treatment groups were statistically significant. Those assigned to




SNAP Change from Baseline to Week 78 Follow-Up

| | Baseline Mean (SD) | Week 34 Mean (SD) | Week 78 Mean (SD) | Week 34 to Week 78 Cohen's d | Baseline to Week 78 Cohen's d |
|---|---|---|---|---|---|
| ATX + PT | 2.22 (.37) | 1.23 (0.77) | 1.39 (.67) | -0.25 | 1.30** |
| ATX Alone | 2.20 (.44) | 1.15 (0.51) | 1.36 (.52) | -0.51* | 1.80** |
| PT + Placebo | 2.23 (.37) | 1.13 (0.48) | 1.39 (.74) | -0.43 | 1.07** |
| Placebo Alone | 2.14 (.48) | 1.42 (0.63) | 1.60 (.48) | -0.36 | 1.00** |
| Whole Sample | 2.19 (.41) | 1.23 (0.61) | 1.43 (.60) | -0.38** | 1.26** |
| Still Taking ATX | 2.14 (0.39) | 0.93 (0.41) | 1.15 (0.53) | -.51* | 1.49** |

HSQ Change from Baseline to Week 78 Follow-Up

| | Baseline Mean (SD) | Week 34 Mean (SD) | Week 78 Mean (SD) | Week 34 to Week 78 Cohen's d | Baseline to Week 78 Cohen's d |
|---|---|---|---|---|---|
| ATX + PT | 3.93 (1.79) | 1.94 (1.68) | 2.21 (1.46) | -0.20 | 1.08** |
| ATX Alone | 3.64 (1.69) | 1.63 (1.19) | 2.04 (1.30) | -0.47* | 1.03** |
| PT + Placebo | 4.14 (1.48) | 1.68 (1.24) | 2.32 (1.60) | -0.64* | 1.28** |
| Placebo Alone | 3.91 (1.76) | 2.52 (1.74) | 3.09 (1.96) | -0.40 | 0.46* |
| Whole Sample | 3.89 (1.67) | 1.93 (1.50) | 2.39 (1.60) | -0.39** | 0.93** |
| Still Taking ATX | 3.59 (1.35) | 1.26 (0.95) | 1.64 (1.06) | -0.50* | 1.29** |

Note: *p<.05, **p<.001. Vertical line at Week 34 indicates end of study treatment. PT=Parent Training, ATX=Atomoxetine, SNAP-IV-C=Swanson, Nolan, and Pelham - IV, HSQ=Home and School Situations Questionnaires, SD= standard deviation.

**FIG. 1.** ADHD symptom scores **(A)** and noncompliance **(B)** over time by original treatment assignment, and by PT versus no PT **(C, D)**, last observation carried forward to week 34. Although some of the week 34 end-of-treatment improvement is lost by week 78 FU, the endpoint remains significantly better than baseline for all originally assigned treatment groups. Those originally assigned placebo had an open atomoxetine trial after week 10 if needed. Difference in change from baseline to week 78 between placebo and 3 pooled active treatments: $p = 0.044$ for SNAP ADHD rating and $p = 0.023$ for HSQ noncompliance score. Change difference between PT and no PT is not significant. Vertical line at week 34 indicates end-of-study treatment. ADHD, attention-deficit/hyperactivity disorder.

Table 2. Drugs Taken at 1.5 Years by Those Available at Follow-Up by Original Treatment Assignment and by Whether They Received Parent Training

| | *Total* | *Drug combinations by 4 treatment groups* | | | | *Parent training* | |
|---|---|---|---|---|---|---|---|
| *Drug* | *(N = 93)*[a] n *(%)* | *ATX+PT (N = 25)*[a] n *(%)* | *ATX (N = 27)* n *(%)* | *PT+placebo (N = 19)* n *(%)* | *Placebo (N = 22)* n *(%)* | *Yes (N = 44)*[a] n *(%)* | *No (N = 49)* n *(%)* |
| No medications | 23 (24.7) | 3 (12.0) | 7 (25.9) | 5 (26.3) | 8 (36.4) | 8 (18.2) | 15 (30.6) |
| Atomoxetine only | 24 (25.8) | 6 (24.0) | 11 (40.7) | 4 (21.1) | 3 (13.6) | 10 (22.7) | 14 (28.6) |
| ATX+another drug | 8 (8.6) | 2 (8.0) | 0 (0.0) | 4 (21.1) | 2 (9.1) | 6 (13.6) | 2 (4.1) |
| Stimulant only | 13 (14.0) | 4 (16.0) | 5 (18.5) | 3 (15.8) | 1 (4.5) | 7 (15.9) | 6 (12.2) |
| Stimulant+any non-ATX drug | 8 (8.6) | 6 (24.0) | 1 (3.7) | 0 (0.0) | 1 (4.5) | 6 (13.6) | 2 (4.1) |
| Other drugs and combinations | 17 (18.3) | 4 (16.0) | 3 (11.1) | 3 (15.8) | 7 (31.8) | 7 (15.9) | 10 (20.4) |
| Same as week 34 end-of-study treatment | 45 (47.9) | 13 (52.0) | 14 (51.9) | 7 (35.0) | 11 (50) | 20 (44.4) | 25 (51) |
| Changed from week 34 to FU | 49 (52.1) | 12 (48.0) | 13 (48.1) | 13 (65.0) | 11 (50) | 25 (55.6) | 24 (49) |

No contrasts were statistically significant.

[a]Marks one subject did not report their medications at 1-year FU. ''Other Drugs'' includes combinations of the following drugs not included in the table: alpha-2-adrenergic agonist, atypical antipsychotics, serotonin reuptake inhibitors, other non-ADHD medications, bupropion.

ATX, atomoxetine; FU, follow-up; PT, parent training.

PT were taking more medication other than ATX than those with no PT, but not significantly so ($U = 927.5$, $p = 0.203$). Of those taking ATX at FU, those who had PT were taking a mean dose of 41.3 mg per day and those without PT were taking 43.9 mg per day, not significantly different ($U = 127.5$, $p = 0.985$).

Table 3 shows clinical outcomes at FU by PT versus no PT. The group assigned to PT had a higher rate of inclusion in regular classrooms ($\chi^2 = 12.606$, $p = 0.04$), also noted at baseline ($\chi^2 = 4.576$, $df = 1$, $p = 0.032$). Table 4 shows use of behavioral techniques at FU by parents who had received PT. These were not significantly associated with either ADHD symptoms or noncompliance when examined in several different ways.

Figure 2 shows change in responder status by assigned treatments from 34-week study-treatment termination to the FU separately for SNAP ADHD symptoms (first panel) and noncompliance (HSQ, second panel), and for response in both domains simultaneously (last panel). Responder status at each assessment point was defined as 30% improvement on the respective scale. Those originally assigned to placebo alone had a lower rate of responders at FU than those assigned to an active treatment: 36% versus 62% for noncompliance response ($\chi^2 = 24.681$, $p = 0.031$) and 27% versus 51% for dual responder status ($\chi^2 = 3.949$, $df = 1$, $p = 0.047$), with a trend for ADHD response: 45% versus 65% ($\chi^2 = 2.774$, $df = 1$, $p = 0.096$), even though placebo nonresponders were treated openly after week 10. Dimensionally, also, those originally assigned placebo alone showed less improvement than the three active treatments (SNAP: $t = -2.039$, $df = 92$, $p = 0.044$; HSQ: $t = -2.903$, $df = 92$, $p = 0.023$). The responder rate was not significantly different between PT and no PT on ADHD ($\chi^2 = 0.524$, $df = 1$, $p = 0.469$), noncompliance ($\chi^2 = 0.30$, $df = 1$, $p = 0.863$), and dual responders ($\chi^2 = 0.024$, $df = 1$, $p = 0.877$).

Table 3. Comparison of Those Originally Assigned Parent Training Versus Others on Services Use and Primary Outcomes at Follow-Up

| *Variable* | *Parent training (N = 45)* | *No parent training (N = 49)* |
|---|---|---|
| Emergency room, *n* (%) | 8 (18.2) | 9 (18.4) |
| Medical hospitalization, *n* (%) | 2 (4.5) | 1 (2.0) |
| Taking medication, *n* (%) | 36 (81.8) | 34 (69.4) |
| 2 or more medications, *n* (%) | 12 (33.3) | 10 (29.4) |
| School placement*, *n* (%) | | |
| Full inclusion | 14 (31.8) | 6 (12.2) |
| Full inclusion with an aid | 12 (27.3) | 15 (30.6) |
| Part-time special education | 5 (11.4) | 9 (18.4) |
| Full-time special education | 9 (20.5) | 7 (14.3) |
| Center-based/self-contained class | 3 (6.8) | 2 (4.1) |
| Home school or cyber school | 1 (2.3) | 4 (8.2) |
| Other | 0 (0.0) | 6 (12.2) |
| Aberrant behavioral checklist, mean (SD) | | |
| Irritability | 10.81 (8.35) | 10.63 (7.85) |
| Social withdrawal | 5.79 (4.74) | 7.68 (6.06) |
| Stereotypic behavior | 3.23 (3.63) | 3.69 (3.74) |
| Hyperactivity | 17.16 (10.30) | 16.94 (9.64) |
| Inappropriate speech | 3.81 (3.52) | 3.78 (2.97) |
| HSQ score, mean (SD) | 2.21 (1.41) | 2.51 (1.70) |
| SNAP-IV, mean (SD) | | |
| Combined | 1.40 (0.70) | 1.47 (0.51) |
| Hyperactive/impulsivity | 1.36 (0.82) | 1.33 (0.64) |
| Inattentive | 1.45 (0.69) | 1.61 (0.55) |

The only significant difference is school placement. One subject (from PT+placebo) did not complete emergency room, medical hospitalization, and medications. Two subjects (1 from ATX + P and 1 from PT+placebo) did not complete ABC. Three subjects (2 from ATX+PT and 1 from PT+placebo) did not complete HSQ.

*$p \leq 0.05$ for school place Fisher's exact test.

ABC, aberrant behavioral checklist; ATX, atomoxetine; HSQ, Home Situations Questionnaire; PT, parent training; SD, standard deviation; SNAP-IV-C, Swanson, Nolan, and Pelham IV.

## Discussion

During the 44-week FU interval from weeks 34 to 78, no systematic treatment was provided by the study; all participants returned to the clinic or other community care from which they had been recruited. In general, the improvement from the original baseline found at week 34 for symptoms of ADHD and noncompliance was largely sustained, as shown in the graphs of the two primary outcome measures (Fig. 1A, B). As expected, there was

Table 4. Use of Behavioral Techniques by Parents Who Received Parent Training

| *Behavioral skills* | *Using skill,* n *(%)* *Total* N = *48*[a] |
|---|---|
| Reinforcement | 34 (70.8) |
| Planned ignoring | 32 (66.7) |
| Behavioral principles | 31 (64.6) |
| Compliance training | 29 (60.4) |
| Prevention strategies I | 27 (56.3) |
| Teaching skills | 27 (56.3) |
| Generalization and maintenance | 23 (47.9) |
| Token economy | 22 (45.8) |
| Time out | 21 (43.8) |
| Prevention strategies II—daily schedule | 20 (41.7) |
| Booster session | 15 (31.3) |
| Crisis management | 10 (20.8) |
| Bedtime and sleep problems | 8 (16.7) |
| Toilet training | 7 (14.6) |
| Functional communication training | 5 (10.4) |
| Imitation skills | 5 (10.4) |
| Feeding skills | 3 (6.3) |
| No behavioral skill used | 3 (6.3) |
| No. of skills used per case, mean (SD) | 10.82 (6.57) |

[a]Three cases from the no parent training groups received parent training after the study treatment and are included in the 48.

SD, standard deviation.

some lessening of the response overall, in conjunction with some drifting away from medication initiated in the study (25% unmedicated at FU, only one-third still taking ATX). The large sustained improvement with so few continuing the original treatment suggests that the improvement depended on more than the original study treatment; additional contributors might be the general access to medical care, neurodevelopmental maturation, other things occurring in the children's life (learning from experience), and/or establishment of virtuous cycles.

A surprising exception to the generally sustained improvement from week 34 to FU was the divergence for those originally assigned to placebo alone. Children assigned to placebo did not enjoy the progress seen in other groups, even though they received active medication between 10 and 34 weeks in the extension if they had not shown a good response. They should theoretically have enjoyed as good a response by 34 weeks and at FU as those assigned to ATX alone. We are not sure what to make of this. The most likely explanation would be happenstance. Possibly there was some failure of randomization such that poor responders happened to be assigned placebo alone. If so, it would suggest that the superiority of active treatment over placebo alone observed at 10 weeks was inflated by chance and the real differential effect was somewhat less. However, demographic and baseline clinical differences between groups were generally not significant, so it is not clear in what way randomization may have assigned children destined to be poorer responders to one group.

One possibility is the significantly lower proportion of the placebo group in special education; they might have had less external support to capitalize on study treatment. (On the other hand, maybe this reflected less disability.) Perhaps going through 10 weeks of placebo without much benefit influenced later treatment expectations, adherence, and willingness to try other treatments. This would be consistent with the fact that a (nonsignificantly) higher proportion of the placebo group was taking no medication at FU. If the same finding was replicated in a substantial number of studies, it could raise ethical issues about assigning placebo. However, broad experience of other studies (Findling et al. 2004) does not suggest an impairment of open treatment response after experiencing placebo, and several authors suggest no harm or even possible benefit from placebo (Vitiello 2003; Derivan et al. 2004; Aman and Farmer 2008; Sandler et al. 2010).

The fact that only one-third of those with FU data continued taking ATX, while 27% had started a stimulant and 13% had started an alpha-2 agonist, suggests that a minority had adequate lasting benefit from ATX. Alternatively, insurance coverage discrimination against ATX or other expense consideration could have contributed to the low retention on ATX. (On a drug-cost website, ATX costs $218–$278 per 30 capsules, depending on size, compared to $177–$184 for 30 caps of mixed amphetamine salts XR and $172–$197 for 30 caps of OROS methylphenidate [Consumer Reports 2012]).

However, it is not unusual for a FU of an randomized control trial (RCT) to find significant drifting from the study medication. For example, the Multimodal Treatment study of Children with ADHD (the MTA) found that after 8 years, only about 10% continued taking a stimulant (Molina et al. 2009). In the Treatment of Severe Childhood Aggression study, only 43% of the augmented treatment group and 36% of the basic treatment group were still taking the study regimen at 1-year FU (Gadow et al. 2016). On the other hand, at the 1-year FU of the RUPP-PI study in ASD, 67% of the combination treatment group and 53% of medication-alone groups were still taking risperidone, the original study medication (Arnold et al. 2016). The 10% taking an antipsychotic in this study suggested that, for some, a different medication was needed, likely because of cooccurring irritability or disruptive behavior.

Contrary to our hopes, those assigned PT did not significantly surpass those without PT by any measure at FU. This is not surprising given the elapsed time and other reports. Although some studies find PT effective for ADHD in children without ASD, especially preschoolers (Webster-Stratton 2011), and in children without cooccurring disorders (Lee et al. 2012), the findings are not clear and consistent. In contrast to the hope for a lasting effect from training parents, a meta-analysis (Lee et al. 2012) found that the posttreatment effects dissipated considerably at FU. They concluded that behavioral contingencies were likely terminated when assistance provided by the therapist ended. Perhaps the ''dose'' or duration of PT in this study (weekly for 10 weeks, then every 4 weeks until week 34) was inadequate for lasting effects. Possibly some booster sessions during the FU interim would have impacted outcome. Indeed, Lee et al's meta-analysis (2012) concluded that FU sessions may be needed to maintain continued contingency techniques at home.

Another study using PT in ASD compared it with psychoeducation in preschool children with moderate levels of disruptive behavior as defined by a score of ≥15 on the Irritability subscale of the ABC. In that study, 79% (48/61) of clinical responders at week 24 continued to be responders at week 48 FU (Bearss et al. 2015). The PT programs had a number of similarities. On average, the parents received three additional PT sessions (10 vs. 7 in CHARTS) over 16 weeks. Perhaps these differences in dose and schedule of delivery were sufficient to have a positive impact. Otherwise, the PT programs were similar in terms of contact, booster sessions, and home visits. Perhaps the age difference and target symptoms were more important. Children in that study (Bearss et al. 2015) were about 3.5 years younger than this one (4.7 vs. 8.1, range 3–0 to 6–11 vs. 5–0 to 14–11 years). Inclusion criteria and target symptoms were also different. Disruptive behaviors like tantrums might be

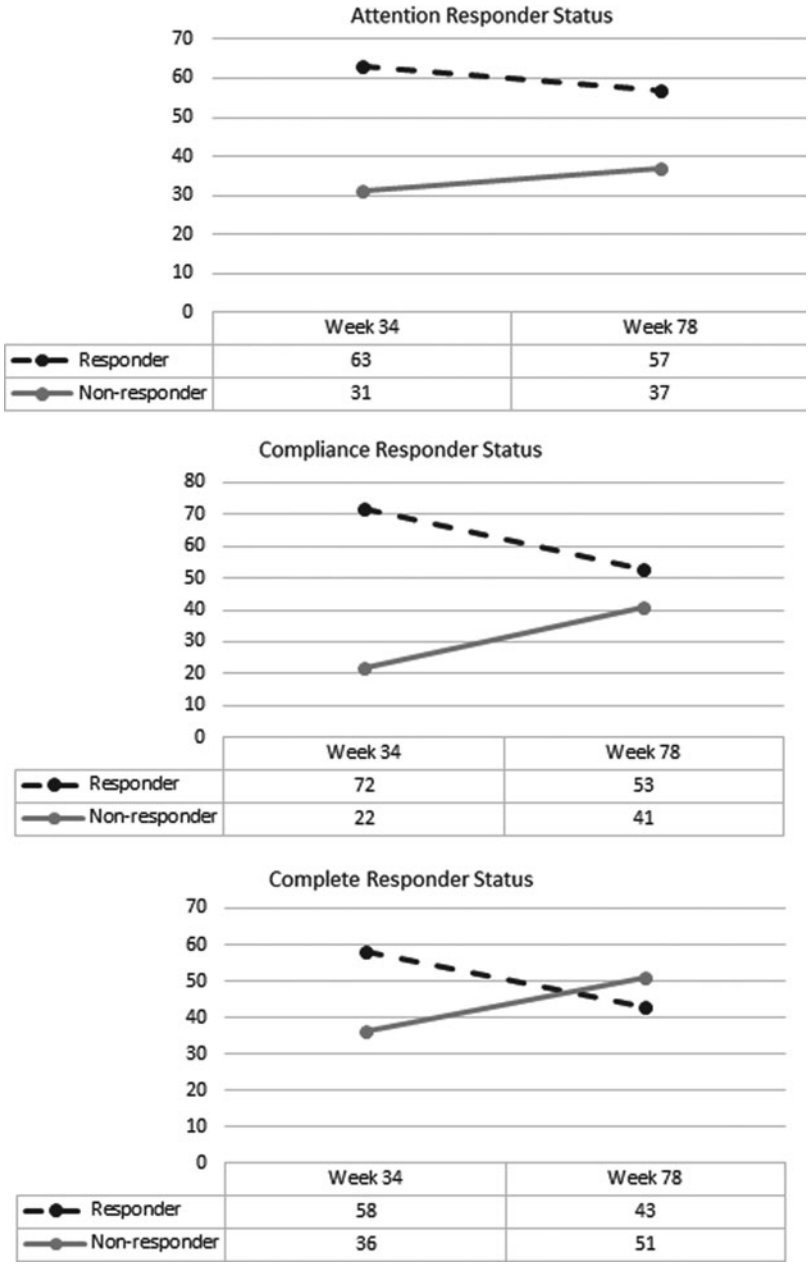



**FIG. 2.** Change in proportion of responders from week 34 to follow-up. Response is defined as >30% improvement in the relevant scale, Swanson, Nolan, and Pelham attention-deficit/hyperactivity disorder symptom ratings for attention responder and Home Situations Questionnaire for compliance responder.

more amenable to change than many symptoms of ADHD. In fact, moderator analyses of that study (Bearss et al. 2015; Lecavalier et al. 2016) indicated that children with significant ADHD symptoms improved much less than their counterparts with fewer ADHD symptoms (Lecavalier et al. 2016). This is important because presence of ADHD symptoms was a prerequisite for this study.

### *Limitations*

Limitations include incomplete retention, although 94/128 (73%) are in the usual range for FUs of randomized clinical trials. Limited power with 94 participants divided into four groups could have left some false negatives. Teacher ratings were not collected for the FU. Finally, had we known beforehand that the original placebo group would fare more poorly at FU, despite the opportunity for an open trial of ATX similar to what the others received, we could have built in special queries to try to determine the *reason* for this outcome. A further need beyond the scope of this article is analysis for moderation and mediation, and we plan an article dedicated to that.

## Conclusions

FU 1.5 years after baseline of this large trial of ATX and PT for children with ASD and ADHD yields the following findings: the 94 available at FU maintained the bulk of their endpoint improvement 10 months after end-of-study treatment, despite the fact that a fourth of them had stopped all medication and only a third continued the

study-initiated ATX. PT made little difference on FU outcome. Although a few who were responders at the 34-week endpoint (>30% improvement on primary outcomes) became nonresponders and some who were not responders at 34 weeks became responders, most maintained their week 34 status. Future research should determine subgroup markers of those who respond (i.e., moderators and mediators) and explore treatments for the ~40% who at FU were not responders on one of the primary outcomes.

## Clinical Significance

Only a minority of children with ASD and ADHD continued taking ATX 1.5 years after starting it, probably related to a low initial response rate. A wide variety of psychopharmacological strategies is needed to meet the needs of ATX nonresponders. Most who do respond to ATX maintain the benefit 1.5 years later. Effects of adding 12 PT sessions appeared to attenuate 1 year after active treatment stopped.

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## References

Altepeter TS, Breen MJ: The Home Situations Questionnaire (HSQ) and the School Situations Questionnaire (SSQ): Normative data and an evaluation of psychometric properties. J Psychoeduc Assess 7: 312–322, 1989.

Aman MG: Annotated bibliography on the aberrant behavior checklist (ABC). 2012. Unpublished manuscript, The Nisonger Center UAP, Ohio State University, Columbus, Ohio. http://psychmed.osu.edu/media/ABC_Annotated_Bibliography.pdf (last accessed April 17, 2018).

Aman MG, Farmer CA: Psychotropic medication research in children and adolescents: Empirical findings and ethical implications. J Empir Res Hum Res Ethics 3:39–47, 2008.

Aman MG, Singh NN, Stewart AW, Field CJ: The aberrant behavior checklist: A behavior rating scale for the assessment of treatment effects. Am J Ment Def 89:485–491, 1985a.

Aman MG, Singh NN, Stewart AW, Field CJ: Psychometric characteristics of the aberrant behavior checklist. Am J Ment Def 489: 492–502, 1985b.

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Health Disorders TR, 4th ed. Washington, DC: American Psychiatric Association; 2000.

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: American Psychiatric Association; 2013.

Arnold LE, Aman MG, Li X, Butter E, Humphries K, Scahill L, Lecavalier L, McDougle CJ, Swiezy NB, Handen B, Wilson K, Stigler KA: RUPP autism network randomized clinical trial of parent training and medication: One-year follow-up. J Am Acad Child Adolesc Psychiatry 51:1173, 2012.

Barkley RA, Edelbrock C: Assessing situational variation in children's problem behaviors: The Home and School Situations Questionnaires. In: Advances in Behavioral Assessment of Children and Families. Edited by Prinz R. Greenwich (Connecticut), JAI Press, Inc., 1987, pp. 157–176.

Barkley RA, Edwards GH, Robin AL: Defiant Teens: A Clinician's Manual for Assessment and Intervention. New York (New York), Guilford Press, 1999, p. 196Y198.

Bearss K, Johnson C, Smith T, Lecavalier L, Swiezy N, Aman M, McAdam DB, Butter E, Stillitano C, Minshawi N, Sukhodolsky DG, Mruzek DW, Turner K, Neal T, Hallett V, Mulick JA, Green B, Handen B, Deng Y, Dziura J, Scahill L: Effect of parent training vs parent education on behavioral problems in children with autism spectrum disorder: A randomized clinical trial. JAMA 313:1524–1533, 2015.

Bussing R, Fernandez M, Harwood M, Wei Hou, Garvan CW, Eyberg SM, Swanson JM: Parent and teacher SNAP-IV ratings of attention deficit hyperactivity disorder symptoms: Psychometric properties and normative ratings from a school district sample. Assessment 15:317–328, 2008.

Chowdhury M, Aman M G, Scahill L, Swiezy N, Arnold LE, Lecavalier L, Johnson C, Handen B, Stigler K, Bearss K, Sukhodolsky D, McDougle: The Home Situations Questionnaire-PDD version: Factor structure and psychometric properties. J Intell Disabil Res 54:281–291, 2010.

Consumer Reports. 2012. http://consumerhealthchoices.org/wp-content/uploads/2012/08/BBD-ADHD-Full.pdf (last accessed April 17, 2018).

Derivan AT, Leventhal BL, March J, Wolraich M, Zito JM: The ethical use of placebo in clinical trials involving children. J Child Adolesc Psychopharmacol 14:169–174, 2004.

Findling RL, Aman MG, Eerdekens M, Derivan A, Lyons B: Long-term, open-label study of risperidone in children with severe disruptive behaviors and below-average IQ. Am J Psychiatry 161:677–684, 2004.

Gadow KD, Brown NV, Arnold LE, Buchan-Page KA, Bukstein OG, Butter E, Farmer CA, Findling RL, Kolko DJ, Molina BS, Rice RR Jr, Schneider J, Aman MG: Severely aggressive children receiving

stimulant medication versus stimulant and risperidone: 12-month follow-up of the TOSCA trial. J Am Acad Child Adolesc Psychiatry 55:469–478, 2016.

Guy W: ECDEU Assessment Manual of Psychopharmacology. Rockville (Maryland), National Institute of Mental Health US Department of Health, Education, and Welfare Publication (ADM), Psychopharmacology Research Branch, 1976, pp. 76–338.

Handen BL, Aman MG, Arnold LE, Hyman SL, Tumuluru RV, Lecavalier L, Corbett-Dick P, Pan X, Hollway JA, Buchan-Page KA, Silverman LB, Brown NV, Rice RR Jr, Hellings J, Mruzek DW, McAuliffe-Bellin S, Hurt EA, Ryan MM, Levato L, Smith T: Atomoxetine, parent training, and their combination in children with autism spectrum disorder and attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 54:905–915, 2015.

Lecavalier L: Behavioral and emotional problems in young people with pervasive developmental disorders: Relative prevalence, effects of subject characteristics, and empirical classification. J Autism Dev Disord 36:1101–1114, 2006.

Lecavalier L, Smith T, Johnson C, Bearss K, Swiezy N, Aman MG, Sukhodolsky DG, Deng Y, Dziura J, Scahill L: Moderators of parent training for disruptive behaviors in young children with autism spectrum disorder. J Abnorm Child Psychol 45:1235–1245, 2016.

Lee PC, Niew WI, Yang HJ, Chen VC, Lin KC: A meta-analysis of behavioral parent training for children with attention deficit hyperactivity disorder. Res Dev Disabil 33:2040–2049, 2012.

Molina BS, Hinshaw SP, Swanson JM, Arnold LE, Vitiello B, Jensen PS, Epstein JN, Hoza B, Hechtman L, Abikoff HB, Elliott GR, Greenhill LL, Newcorn JH, Wells KC, Wigal T, Gibbons RD, Hur K, Houck PR; MTA Cooperative Group: The MTA at 8 years: Prospective follow-up of children treated for combined-type ADHD in a multisite study. J Am Acad Child Adolesc Psychiatry 48:484–500, 2009.

Mullen EJ: Mullen Scales of Early Learning. Bloomington (Minnesota), Pearson Assessments; 1989.

Roid GH: Stanford-Binet Intelligence Scales, 5th ed. Itasca (Illinois), Riverside Publishing; 2003.

Rutter M, Le Couteur A, Lord C: Autism Diagnostic Interview Revised. Torrance (California), Western Psychological Services; 2003.

Sandler AD, Glesne CE, Bodfish JW: Conditioned placebo dose reduction: A new treatment in attention-deficit hyperactivity disorder? J Dev Behav pediatr 31:369–375, 2010.

Silverman L, Hollway JA, Smith T, Aman MG, Arnold LE, Pan X, Li X, Handen BL: A multisite trial of atomoxetine and parent training in children with autism spectrum disorders: Rationale and design challenges. Res Autism Spectr Disord 8:899–907, 2014.

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. J Am Acad Child Psychiatry 47:921–929, 2008.

Smith T, Aman MG, Arnold LE, Silverman LB, Lecavalier L, Hollway J, Tumuluru R, Hyman SL, Buchan-Page KA, Hellings J, Rice RR Jr, Brown NV, Pan X, Handen BL: Atomoxetine and parent training for children with autism and attention-deficit/hyperactivity disorder: A 24-week extension study. J Am Acad Child Adolesc Psychiatry 55:868.e862–876.e862, 2016.

Tumuluru RV, Corbett-Dick P, Aman MG, Smith T, Arnold LE, Pan X, Buchan-Page KA, Brown NV, Ryan MM, Hyman SL, Hellings J, Williams C, Hollway JA, Lecavalier L, Rice Jr., RR, McAuliffe-Bellin S, Handen BL Adverse events of atomoxetine in a double blind placebo controlled study in children with autism. J Child Adolesc Psychopharmacol 27:708–714, 2017.

Vitiello B: Ethical considerations in psychopharmacological research involving children and adolescents. Psychopharmacology 171:86–91, 2003.

Webster-Stratton C: Combining parent and child training for young children with ADHD. JCCAP 40:191–203, 2011.

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