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Pharmacotherapy of the Preschool ADHD Treatment Study (PATS) Children Growing Up

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Abstract

Objective—To describe the long-term psychopharmacological treatment of children first diagnosed with attention-deficit/hyperactivity disorder (ADHD) as preschoolers.

Method—In a systematic, prospective, naturalistic follow-up, 206 (68.0%) of the 303 children who participated in the Preschool ADHD Treatment Study (PATS) were reassessed 3 years (mean age 7.4 years), and 179 (59.1%), 6 years (mean age 10.4 years), after completion of the controlled study. Pharmacotherapy and clinical data were obtained from the parents. Pharmacotherapy was defined as use of a specific class of medication for at least 50% of the days in the previous 6 months.

Results—At year 3, 34.0% were on no pharmacotherapy, 41.3% were on stimulant monotherapy, 9.2% on atomoxetine, alone or with a stimulant, 8.3% on an antipsychotic, usually together with a stimulant, and the remaining 7.2% on other pharmacotherapy; overall, 65.0% were on an indicated ADHD medication. At year 6, 26.8% were on no pharmacotherapy, 40.2% were on stimulant monotherapy, 4.5% on atomoxetine, alone or with a stimulant, 13.4% on an antipsychotic, and 15.1% on other pharmacotherapy; overall, 70.9% were on an indicated ADHD medication.

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Antipsychotic treatment was associated with more comorbidity, in particular disruptive behavior disorders and pervasive development disorders, and a lower level of functioning.

Conclusion—The long-term pharmacotherapy of preschoolers with ADHD was heterogeneous. While stimulant medication continued to be used by most children, about 1 child in 4 was off medication, and about 1 in 10 was on an antipsychotic.

Keywords

ADHD; preschoolers; medication; stimulant

Introduction

The hyperactive/impulsive and combined types of attention-deficit/hyperactivity disorder (ADHD) are usually first diagnosed and treated when the child enters elementary school. ADHD symptoms, however, are often present in preschool years, and, when severe and functionally impairing, can lead to clinical referral and treatment under age 6. The Preschool ADHD Treatment Study (PATS) was a controlled clinical trial that found methylphenidate to be efficacious in decreasing ADHD symptoms in preschoolers aged 3-5.5 years with severe ADHD.[1] Psychiatric diagnoses in preschoolers tend to be fairly stable.[2,3] A longitudinal follow-up of PATS has documented that ADHD diagnosed in preschool persists through the school-age years and requires long-term treatment.[4]

Little is known about the long-term pharmacotherapy course of children first treated with methylphenidate for ADHD in their preschool years. In particular, it is unknown if stimulant medication is continued or if other medications are substituted for, or added to it, in clinical practice. This information can be of interest to clinicians treating young children with ADHD, parents inquiring about the type and duration of treatment, and researchers studying the developmental psychopharmacology of ADHD.

Consistent with a general approach to preschool ADHD that uses behavior therapy through parent training as first-line treatment while reserving pharmacotherapy for severe and non-responsive cases,[5] the PATS sample was selected for severity and pervasiveness of ADHD symptoms, and behavior management training was provided before considering medication.[6] After the end of the controlled trial, children received community treatment and were systematically reassessed 3 and 6 years after the original enrollment in PATS.

We analyzed this naturalistic follow-up database and examined the pharmacotherapy received in the years after completing PATS. The purpose was to document the type of pharmacotherapy received by these children as a way of better understanding their treatment needs over time. The approach was descriptive and aimed at addressing the following main questions: 1) How common was long-term stimulant monotherapy? 2) How common was combined pharmacotherapy? 3) Which medications other than stimulants were used? 4) Was the type of pharmacotherapy associated with certain patient characteristics? We expected that stimulant medication would continue to be a main treatment component during school years, and also that the pharmacotherapy would become more complex in order to address

the emergence of other psychopathology, such as disruptive behavior, anxiety, and mood disorders.

Method

Study Design

This was a systematic, open, prospective follow-up of the children who had participated in the PATS, a multiphase clinical trial that tested the efficacy and safety of methylphenidate for the treatment of children aged 3.0-5.5 years with hyperactive/impulsive or combined-type ADHD. The rationale, design, methods, and results of the PATS have been extensively reported.[1,6–8] In brief, 303 preschool-age children meeting strict criteria for pervasive and impairing symptoms of ADHD were enrolled in PATS. Non-responders to initial parent training in behavior management qualified for the pharmacotherapy phases, which included, sequentially, a safety lead-in, a placebo-controlled cross-over efficacy clinical trial, a placebo-controlled parallel-group efficacy clinical trial, an open-label maintenance phase, and a placebo-controlled discontinuation clinical trial. The flow through the study was flexible based on clinical presentation.[6] At the end of PATS, the participants were referred for continuing treatment in their community and periodically returned to the research centers for observational follow-up assessments.

Participants

All the children initially enrolled in PATS were eligible for the follow-up study, which was approved by the institutional review board of each of the 6 clinical research sites (Columbia University, Duke University Medical Center, Johns Hopkins University, New York University, University of California, Irvine, and University of California, Los Angeles). All parents provided written permission, and the children gave verbal assent to participating in the follow-up study.

Of the 303 children who had met the PATS entry criteria at a mean age of 4.4 years, data about subsequent pharmacotherapy could be obtained for 206 (68.0%) children at the year 3 follow-up assessment and for 179 children (59.1%) at the year 6 follow-up assessment. Their demographics are summarized in Table 1. No differences were found between the 179 children with pharmacotherapy data at year 6 and the other PATS children for whom such data were not available, with respect to age, sex, IQ, ethnicity, family composition, parental education, public assistance, scores on the Clinical Global Impressions Scale (CGI), Children’s Global Assessment Scale (CGAS), or teacher and parent Conners' Rating Scales (CRS) hyperactive/impulsive and total scores, as assessed at baseline entry in PATS.

Assessments

At the year 3 and year 6 follow-up visits, children received a comprehensive clinical evaluation, which included child examination, parental interview, and review of teacher rating scales. Methods of the clinical assessment and diagnostic findings have been reported in detail.[4] The diagnostic evaluation included the administration of the Diagnostic Interview Schedule for Children (DISC)-Parent Report, parent and teacher versions of the CRS-Revised-Long Version, the PATS Diagnostic Interview, and the CGAS. The diagnostic

information was systematically reviewed during multisite consensus conference calls to ensure reliability and validity of the diagnoses. As part of the assessments, parents were queried about use of psychiatric medications since the previous visit, including type of medication, dose, and duration of use, with the Services Use in Children and Adolescents-Parent Interview (SCA-PI).[9]

Data Analyses

For a child to be considered in treatment with a particular class of medication, the child had to have received that type of medication for at least 50% of the time in the 6 months prior to the assessment. Designation of medication use in more than one class required surpassing the 50% threshold for each individual class during the 6-month window (but not necessarily simultaneously). Psychiatric medications were classified into the following categories: stimulants (i.e., methylphenidate and amphetamine products), norepinephrine reuptake inhibitors (i.e., atomoxetine), alpha-2-agonists (i.e., clonidine, guanfacine), selective serotonin reuptake inhibitors (SSRIs), non-SSRI antidepressants (e.g., bupropion, tricyclics), antipsychotics, mood stabilizers (e.g., lithium, divalproex, carbamazepine, oxcarbazepine, topiramate, lamotrigine), anxiolytics (e.g., buspirone), and hypnotics (e.g., melatonin, zolpidem, diphenhydramine).

Descriptive statistics were applied to the data. Between-group comparisons were conducted on the year 6 medication status subgroups, and children on antipsychotics were compared to those not on antipsychotics. For continuous variables, normality and homogeneity of variance were examined both graphically and by testing. When homogeneity of variance was rejected, Welch's analysis of variance (ANOVA) was used. When sample size was diminished for one of the groups (as in the two-group testing)—and the test for homogeneity of variance did not reveal significant evidence in support of heterogeneity—the Kruskal-Wallis nonparametric test results were utilized. For categorical variables, contingency table χ^2 square analyses or exact tests were employed, as appropriate.

Logistic regression analyses were conducted to search for possible predictors of the child being on stimulant monotherapy at the end of the follow-up (year 6 assessment), or on an antipsychotic at either assessment point. The following preschool baseline variables were examined: gender, ethnicity, IQ, ADHD severity (measured with the Conners' parent *DSM-IV* total combined-type T score), number of comorbidities, and parental stress (using the Parental Stress Inventory score).

All analyses were considered exploratory rather than hypothesis-testing, and a two-tailed $p<.05$ was considered significant, with no correction for multiple comparisons.

Results

Pharmacotherapy at Years 3 and 6

At year 3, 34.0% of the 206 assessed children were not receiving pharmacotherapy (based on the study definition of having received a medication for at least 50% of the days in the previous 6 months), 41.3% were on stimulant monotherapy, 6.3% on a stimulant in combination with another ADHD medication, 5.3% on atomoxetine monotherapy, 2.4% on

stimulant in combination with an antidepressant, 8.3% on an antipsychotic, usually in combination with another medication, and the remaining 2.4% on other pharmacotherapy (Table 2). Of the 70 children in the no-medication group, 11 had received some medication in the previous 6 months, but below the threshold of 50% of the time required for pharmacotherapy status. Overall, 65.0% of the year-3 children were on an indicated ADHD medication (i.e., stimulant, atomoxetine, or alpha-2-agonist). In particular, 58.7% were on stimulant medication.

At year 6, 26.8% of the 179 assessed children were not receiving pharmacotherapy, 40.2% were on stimulant monotherapy, 5.6% on a combination of stimulant and another ADHD medication, 3.4% on atomoxetine monotherapy, 5.0% on stimulant in combination with an antidepressant, 13.4% on an antipsychotic, usually in combination with another medication, and the remaining 5.6% on other pharmacotherapy (Table 2). Of the 48 children in the no-pharmacotherapy group, 3 had received some medication in the previous 6 months but below the threshold of 50% of the time required for pharmacotherapy status. Overall, 70.9% of year-6 children were on an indicated ADHD medication (65.3% on stimulant medication).

Females were less likely than males to be on medication at year 6 (OR=2.21, 95% CI 1.07-4.52, χ^2=4.7, df=1, p=.029). There was no association between gender and being on no medication at year 3.

Stimulant monotherapy was the most common pharmacotherapy, accounting for about 62.5% of those on medication at year 3, and 55.5% of those on medication at year 6 (Table 2). Combined pharmacotherapy was observed in 17.9% of the children at year 3, and 27.9% at year 6; this increase was statistically significant (χ^2=5.4, df=1, p=.020).

Considering the type of medications received (i.e., stimulant, norepinephrine reuptake inhibitor, alpha-2-agonist, SSRI, other antidepressant, antipsychotic, mood stabilizer, anxiolytic, and hypnotic), 59% (n=104) of the children who were assessed at both years 3 and 6 (n=177) maintained the same pharmacotherapy profile over time. In particular, 85% (n=93) of the 110 children on stimulants at year 3 continued to receive a stimulant at year 6.

Table 3 reports the demographics and clinical characteristics of the children divided according to year-6 medication status into four groups: no pharmacotherapy, stimulant medication only, antipsychotic medication (either monotherapy or in combination with other psychotropic), and other pharmacotherapy. The four groups differed as to number of comorbid diagnoses (p<.001), rate of pervasive developmental disorders (PDD; p=.046), inattention symptom T scores at PATS entry (p=.048), and CGAS score at year 6 (p=.033; Table 3).

Logistic regression analyses using gender, ethnicity, IQ, ADHD severity, number of comorbidities, and parental stress did not detect any specific predictor of being on stimulant monotherapy at year 6 (global model likelihood ratio chi-square =9.0, df=6, p=.171), or on antipsychotic at year 3 or 6 (global model likelihood ratio chi-square=108.7, df=6, p<.001, but with no statistical significance for any of the individually examined variables).

Antipsychotics

A total of 32 children were treated with antipsychotic medication at year 3 (n=17) and/or year 6 (n=24). Of them, 9 had documented antipsychotic use at both year-3 and -6 assessments (Table S1, available online). Risperidone was the most commonly used antipsychotic (n=22), with the maintenance daily dose ranging from 0.15 to 4 mg (median 1 mg, mean 1.3 ± SD 1.2). Other antipsychotics were quetiapine (7 children; daily dose 25-250 mg, median 200 mg), aripiprazole (5 children; daily dose 3-10 mg, median 5 mg), and ziprasidone (1 child, daily dose 40 mg). Two children who were on risperidone at the year-3 assessment had switched to aripiprazole by the year-6 assessment, and one child on quetiapine at the year-3 assessment was on risperidone at the year-6 assessment. Most antipsychotic use was in combination with a stimulant (Table 2). Of the 17 children on antipsychotics at year 3, 9 were still on antipsychotics at year 6, while 6 had discontinued (2 others were lost to follow-up).

Current and past diagnoses (in addition to ADHD) of the children on antipsychotics are reported in Table S1, available online. Only one of the 32 children had a diagnosis of psychotic disorder, and another had a diagnosis of bipolar disorder. Compared with children not receiving antipsychotics at year 6, children on antipsychotics had more comorbid diagnoses ($p<.0001$), a higher rate of PDD ($p=.025$), oppositional defiant disorder (ODD) or conduct disorder (CD) ($p=.008$), and lower level of global functioning both as preschoolers ($p=.040$) and at school age ($p=.013$). Eleven of the 24 children on antipsychotic treatment at year 6 had a history of a tic disorder, a rate (45.8%) greater than that observed among the children who were not on antipsychotics (16.8%) ($\chi^2=10.7$, df=1, $p=.003$).

Discussion

This study was a systematic follow-up of the naturalistic treatment of children diagnosed with hyperactive/impulsive or combined-type ADHD who had participated in the PATS, a controlled clinical trial of methylphenidate. After completing the controlled phases of PATS, the children were referred to continue treatment in the community. Most of them were assessed 3 and 6 years after originally entering PATS. About 75% of this sample was male and white, with low rate of public assistance and high rate of college-educated parents and two-parent families (Table 1), suggesting that these were not socioeconomically or family-structure distressed families.

The pharmacotherapy ranged from none (34.0% at year 3 and 26.8% at year 6) to stimulant monotherapy (41.3% at year 3 and 40.2% at year 6), antipsychotic medication (8.3% at year 3 and 13.4% at year 6), and a variety of other psychotropics, such as alpha-2-agonists, antidepressants, and mood stabilizers (Table 2). Thus, even though all these children had, in preschool years, met the same stringent entry criteria for participation in PATS, there was considerable inter-subject heterogeneity in pharmacotherapy course in the following years. Between years 3 and 6, however, most (59%) of the children maintained the same pharmacotherapy profile of class of medication, and 85% of the children on a stimulant medication at year 3 continued receiving a stimulant at year 6.

The year-6 data indicate that stimulant medication continued to be utilized by about two-thirds (65.3%) of the children (now aged, on average, 10.4 years), in most cases as a monotherapy. However, about one quarter of the children were not on pharmacotherapy (defined as use of a medication for at least 50% of the time in the past 6 months), and 13.4% were on an antipsychotic, usually in combination with a stimulant. Overall, the use of any indicated ADHD medication varied little from year 3 to year 6, with 65.0% of year-3 and 68.7% of year-6 children receiving medication approved for the treatment of ADHD. These rates are similar to the 71% stimulant use seen in the two medication groups from the Multimodal Treatment of ADHD study (MTA) at the year-3 follow-up.[10]

The use of antipsychotics in this sample is consistent with a recently reported 11.5%-point prevalence in youths with ADHD.[11] In our prospective follow-up, antipsychotic use was often time limited, as less than a third of the 32 children treated with antipsychotics had documented use of antipsychotics at both years 3 and 6 (Table S1, available online). That only one of the children on antipsychotics had received a diagnosis of psychotic disorder is also consistent with pharmacoepidemiological reports that these medications are mainly used to manage non-psychotic conditions.[12] A review of the diagnoses associated with antipsychotic use reveals the complexity of the underlying psychopathology and indicates that antipsychotics were used to manage complex and challenging clinical situations.

The association between antipsychotic use and presence of a PDD (corresponding to the recently introduced *DSM-5* nosological category of autism spectrum disorder)[13] is also relevant, as antipsychotics are effective in the management of severe mood and behavioral disturbances in autism. Risperidone and aripiprazole have a specific pediatric indication approved by the Food and Drug Administration for the treatment of irritability in children with autism.[14] Of interest is the greater prevalence of tic disorders among children on antipsychotics, as it further documents the neuropsychiatric complexity of these patients. Finally, the average daily dose of risperidone (1.3 mg) was similar to that reported in a recent clinical trial of risperidone in children with ADHD aged 6-12 years.[15]

Regardless of pharmacotherapy, the study sample was on average functionally impaired, as shown by CGAS scores on average below 60, with greater impairment in the group on antipsychotics (Table 3). These data underscore the persistent difficulties evidenced by children in this sample diagnosed with ADHD during preschool years, with long-term implications for global functioning.[4] Only one child met criteria for bipolar disorder, suggesting that this disorder is rather infrequent before puberty among children with severe preschool ADHD. Noteworthy is the presence of a PDD in about 10% of the children at year 6 (Table 3). Under the *DSM-IV* diagnostic system used when PATS was conducted, PDD was an exclusion criterion for the diagnosis of ADHD.[16] Accordingly, PATS did not enroll preschoolers meeting criteria for PDD.[1] Thus, evidence of PDD, most frequently Asperger's disorder, had emerged in subsequent years. Previous research found methylphenidate to be effective for children with ADHD in the context of PDD, but with lower efficacy (49% improvement rate) and tolerability than in ADHD without PDD.[17] As might be expected, we found a higher prevalence of PDD in the group treated with antipsychotics (25.0%), as compared to the group on stimulant monotherapy (5.6%, Table 3).

Combined treatment ("polypharmacy") was relatively common and increased with time between years 3 and 6, involving about a quarter of the sample at the year-6 assessment (Table 2). Concerns have been raised about psychotropic polypharmacy in children in light of the dearth of supporting controlled investigations.[18] However, the current evidence-base for combined therapy in the treatment of ADHD is limited to the use of stimulants and alpha-2 agonists, and few studies have evaluated the efficacy and safety of other combinations.[19,20]

A number of important limitations must be taken into account in interpreting these data. As previously discussed, this was a research sample that was not epidemiologically derived but originally selected for participation in a clinical trial and subsequently referred for community treatment. While most of the sample was retained and assessed through year 6, more than a third was lost to follow-up. Medication data were obtained exclusively from parental report, and pharmacy records, pill counts, or other measures of adherence were not available. Another limitation to assessing trajectories of pharmacotherapy comes from the database including only two observation points. No information was available about medication settings, such as pediatric versus psychiatric practice, or public versus private practitioner. Finally, the database for these analyses did not include information on concomitant psychosocial therapies the children might have received in their community, or sufficient detail for reconstructing the rationale behind the individual treatment decision-making. Despite these limitations, the study informs on the long-term pharmacotherapy of children with severe ADHD in preschool.

In conclusion, these data indicate that most children who were diagnosed with ADHD and treated with methylphenidate in preschool continue to use stimulant medication in subsequent school years. There is, however, considerable heterogeneity in their long-term course of pharmacotherapy, with about 1 in 4 of the children at age 10 receiving no consistent pharmacotherapy, and 1 in 10 being on an antipsychotic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Preschool Attention-Deficit/Hyperactivity Disorder (ADHD) Treatment Study (PATS) Medication Follow-Up: Sample Characteristics at Years 3 and 6

	Year 3 (n=206)		Year 6 (n=179)	
Age, mean (SD)	7.4	(0.97)	10.4	(0.99)
Gender, n (%)				
Male	154	(74.8)	133	(74.3)
Female	52	(25.2)	46	(25.7)
Ethnicity, n (%)				
Hispanic or Latino	40	(19.4)	30	(16.8)
Non-Hispanic or -Latino	166	80.6	149	(83.2)
Race,[a] n (%)				
White	159	(77.2)	134	(74.9)
Black or African American	44	(21.4)	37	(20.7)
American Indian/Alaskan Native	14	(6.8)	14	(7.8)
Asian	3	(1.5)	5	(2.8)
Native Hawaiian/Pacific Islander	2	(1.0)	0	(0)
Other	17	(8.3)	17	(9.5)
Public assistance, n (%)	23	(11.2)	10	(5.6)
Parent(s) with college or higher degree,[b] n (%)	141	(69.5)	132	(75.4)
Family composition, n (%)				
2 parental figures	159	(77.2)	134	(74.9)
1 parental figure	45	(21.8)	41	(22.9)
N/A -missing	2	(1.0)	4	(2.2)
C-GAS, [c] *mean (SD)*	53.7	(10.1)	56.5	(10.07)
Comorbidity,[d] n(%)				
ODD/CD	85	(41.7)	60	(33.7)
Anxiety disorder[e]	31	(15.2)	37	(20.1)
Mood disorder	18	(8.8)	15	(8.4)
PDD	12	(5.9)	16	(6.0)
Psychotic disorder	1	(0.5)	2	(1.1)

Note: CD = conduct disorder; CGAS = Children's Global Assessment Scale; ODD = oppositional defiant disorder; PDD = pervasive developmental disorder.

[a] Some participants endorsed more than one race

[b] Three missing at year 3 and 4 at year 6

[c] 2 missing at year 3 and 1 at year 6

[d] Comorbidity data were missing for 2 children at year 3 and 1 child at year 6

[e] Excluding specific phobia

Table 2

Psychopharmacotherapy at Years 3 and 6 Follow-Up

	Year 3 n=206 (100%)		Year 6 n=179 (100%)	
	n	%	n	%
Pharmacotherapy[a]				
None[b]	70	34.0	48	26.8
Stimulant monotherapy[c]	85	41.3	72	40.2
Atomoxetine monotherapy	11	5.3	6	3.4
Stimulant and atomoxetine only	8	3.9	2	1.1
Stimulant and alpha-2-agonist only	5	2.4	8	4.5
Antipsychotic	17	8.3	24	13.4[d]
Monotherapy	2	1.0	2	1.1
With stimulant only	7	3.4	10	5.6
With stimulant plus other medication	7[e]	3.4	9[f]	5.0
With other non-stimulant medication	1[g]	0.5	3[h]	1.7
Stimulant with antidepressant	5[i]	2.4	9[j]	5.0
Stimulant with anxiolytic or hypnotic	4	1.9	5	2.8
Other pharmacotherapy	1[k]	0.5	5[l]	2.8

[a] Pharmacotherapy status is based on medication use for at least 50% of the days in the 6 months prior to the assessment. Eleven children at year 3 and 3 children at year 6 had received some pharmacotherapy below the specified threshold.

[b] 9 children at year 3 and 3 children at year 6 took medication for brief periods without reaching the >50% prespecified threshold for sustained pharmacotherapy used in these analyses.

[c] 78.8% on methylphenidate and 22.2% on amphetamine at year 3, and 79.2% on methylphenidate and 20.8% on amphetamines at year 6.

[d] Not significantly different than at year 3 (χ^2=2.6, df=1, p=.10).

[e] Two children on antipsychotic, stimulant, and mood stabilizer; 1 on antipsychotic, stimulant, alpha-2-agonist, mood stabilizer, and selective serotonin reuptake inhibitor (SSRI); 1 on antipsychotic, stimulant, and atomoxetine; 1 on antipsychotic, simulant, and SSRI; 1 on antipsychotic, stimulant, atomoxetine, and antidepressant; and 1 on antipsychotic, stimulant, and alpha-2-agonist.

[f] Six children on antipsychotic, stimulant, and antidepressant; 1 on antipsychotic, stimulant, and mood stabilizer; 1 antipsychotic, stimulant, and alpha-2-agonist; 1 on antipsychotic, stimulant, alpha-2-agonist, SSRI, and sleep inducer.

[g] One child on antipsychotic and atomoxetine.

[h] Two children on antipsychotic and alpha-2-agonist; 1 on antipsychotic and mood stabilizer.

[i] SSRI in 5 cases; 1 also on mirtazapine.

[j] SSRI antidepressant in 8 cases; 1 also receiving hypnotic and 1 also on atomoxetine.

[k] One child on alpha-2-agonist monotherapy.

[l] One child on SSRI monotherapy; 1 on alpha-2-agonist and SSRI; 1 on stimulant and mood stabilizer; 1 atomoxetine and alpha-2-agonist; 1 on atomoxetine, stimulant, and alpha-2-agonist.

Table 3

Patient Subgroups by Medication Status at Year 6 Follow-Up (n=179)[a]

	No medication	Stimulant Only	Antipsychotic[b]	Other
n	**48**	**72**	**24**	**35**
Age, *mean (SD)*	10.2 (0.94)	10.3 (1.06)	10.5 (0.70)	10.6 (1.08)
Sex, *n* (%)				
Male	30 (62.5)	59 (81.9)	20 (83.3)	24 (68.6)
Female	18 (37.5)	13 (18.1)	4 (16.7)	11 (31.4)
Race,[c] *n* (%)				
White	35 (76.1)	50 (71.4)	19 (82.6)	30 (85.7)
Black	14 (30.4)	13 (18.6)	6 (26.1)	4 (11.4)
American Indian/Native Alaskan	5 (10.9)	6 (8.6)	1 (4.3)	2 (5.7)
Asian	1 (2.2)	2 (2.9)	1 (4.3)	1 (2.9)
Other	4 (8.7)	8 (11.6)	2 (8.7)	3 (8.6)
IQ, *mean (SD)*	97.7 (14.91)	100.0(16.63)	96.0 (15.19)	99.1 (17.51)
At PATS entry, mean (SD)				
CGI severity	4.7 (0.63)	4.7 (0.56)	4.9 (0.54)	4.7 (0.68)
CGAS	48.3 (5.49)	47.7 (3.91)	**46.2 (3.65)***	47.5 (4.0)
Conners' Inattentive	76.4 (11.33)	72.4 (10.77)	74.3 (12.18)	77.9 (10.8)
Conners' Hyperactive	80.9 (7.81)	77.6 (7.35)	77.7 (7.16)	78.1 (8.71)
Conners' Total	80.4 (8.55)	76.9 (8.14)	77.9 (8.84)	79.6 (8.7)
Current Conners' ADHD rating, mean (SD)				
Inattentive	63.4 (14.98)	61.0 (10.85)	66.0 (13.11)	65.5 (11.17)
Hyperactive	68.9 (13.69)	64.4 (11.25)	69.8 (12.52)	69.7 (13.07)
Total	66.9 (14.4)	63.7 (10.47)	69.1 (12.77)	68.9 (11.88)
Current or historical diagnosis, n(%)				
ODD/CD	32 (66.7)	49 (68.1)	**22 (91.7)***	24 (68.6)
Mood disorder	7 (14.6)	9 (12.5)	6 (25.0)	8 (22.9)
Anxiety disorder [d]	14 (29.2)	22 (30.6)	12 (50.0)	14 (40)
PDD diagnosis	3 (6.3)	4 (5.6)	**6 (25.0)***	6 (17.1)
History of psychosis	1 (2.1)	2 (2.8)	2 (8.3)	1 (2.9)
Diagnoses ever received, cumulative n, *mean (SD)*	3.0 (2.15)	2.9 (1.59)	**4.9 (2.22) *** **	3.5 (2.19)
Current CGAS, *mean (SD)*	58.0 (10.66)	57.8 (9.46)	**52.0 (10.11)***	54.9 (9.69)

Note: "Current" also refers to most recent. Variables with statistically significant difference are bolded. ADHD = attention-deficit/hyperactivity disorder; CD = conduct disorder; CGAS = Children's Global Assessment Scale; CGI = Clinical Global Impression; ODD = oppositional defiant disorder; PATS = Preschool ADHD Treatment Study; PDD = pervasive developmental disorder.

[a]The four groups differed in number of comorbid diagnoses (Kruskal-Wallis chi-square=17.60, p=.0005); PDD rate (exact likelihood ratio chi-square =8.74, omnibus test p=.046); Conners' Inattention score at entry into PATS (Kruskal-Wallis chi-square=7.89, p=.048); and CGAS score at year 6 (Kruskal-Wallis chi-square=8.73, p=.033).

[b] In a two-way comparison of the antipsychotic vs. non-antipsychotic groups, the antipsychotic group had more comorbidities (Kruskal-Wallis chi-square=15.39, p<.0001); higher rate of PDD (exact chi-square=6.05, p=.025) and ODD/CD (likelihood ratio chi-square=7.04, p=.008); and lower CGAS scores both at PATS entry (Kruskal-Wallis chi-square= 4.20, p=.040) and at year 6 (Kruskal-Wallis chi-square=6.16, p=.013).

[c] It adds up to >100% because participants could endorse more than one race.

[d] Other than specific phobia.

* p<.05;

*** p<.001 (children on antipsychotic vs. children not on antipsychotic)