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Stimulant Medications and Cognition, Behavior, and Quality of Life in Children and Youth with HIV

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Abstract

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Background—Limited empirical investigation exists into longitudinal changes in cognition, behavior, or quality of life (QOL) in children with perinatal HIV who are prescribed stimulants.

Methods—This study was an analysis of longitudinal data from children age 3-19 years, with perinatal HIV infection, with and without prescriptions for stimulant medications (prescription [PG] and comparison [CG] groups, respectively), matched on age, availability of CD4%, and outcome measures of cognition, behavior, and QOL. Generalized estimating equation models were used to evaluate effects of stimulant exposure on change in measured outcomes over three years of follow-up, adjusting for baseline levels of outcomes and relevant covariates.

Results—Children in both the PG (n=132) and CG (n=392) obtained mean Verbal and Performance (nonverbal) Intelligence Quotients (VIQ and PIQ, respectively) in the low-average range for age. At baseline, those in PG demonstrated more frequent signs of hyperactivity, impulsivity, and conduct and learning problems than those in CG (p = 0.003 in unadjusted analyses). At follow-up, after adjustment for baseline functioning and other relevant covariates, there were no significant changes from baseline in VIQ or PIQ. Stimulant prescription use, however, was associated with worsening symptoms of hyperactivity (p=0.01), impulsivity (p=0.04), and learning problems (p<0.001) and worsening of perceived health status (p<0.001).

Conclusions—The results suggest expectations for behavioral improvement may not align well with long-term effects of stimulant prescription use on behavior and QOL in children with HIV. Further research is necessary to determine if there are subsets of children who may benefit from stimulant therapy.

Keywords

HIV/AIDS; children; adolescents; ADHD; stimulants

Introduction

Children and adolescents with perinatally acquired human immunodeficiency virus infection (PHIV) may experience multiple risks to mental health and quality of life (QOL), including viral infection of the central nervous system, viral and drug exposure *in utero*, poverty, unstable housing, parental physical and mental health problems, and inadequate support networks.¹⁻² Recent data from US-based cohorts suggest that children and adolescents with PHIV perform within the low-average to average range of intellectual ability and show higher than expected rates of behavioral impairment.³⁻⁹ From infancy through adolescence, PHIV infection is associated with poorer QOL.¹⁰⁻¹³ Youth with PHIV are at risk for clinically significant behavioral problems such as overactivity, impulsivity, and inattention,¹⁻² which may affect academic learning, social relationships, and adherence to treatment regimens. Appropriate therapy for such symptoms is critical to their health care and development, and medications are frequently the first-line treatment choice.¹⁴⁻¹⁶

Stimulant medications are commonly prescribed for children with PHIV and other chronic illnesses for indications varying from treating attention-deficit/hyperactivity disorder (ADHD) and augmenting antidepressants to management of illness-related fatigue and decreased motivation to engage in medical care.¹ A large study indicated that 19% of children with PHIV had been prescribed a stimulant medication.¹⁷ While stimulants are

known to be effective in treating the symptoms of hyperactivity and impulsivity associated with ADHD in children and adolescents across a wide range of cognitive ability,^{15,18-21} it is unclear whether this efficacy is generalizable to children with PHIV. There has been little empirical investigation into longitudinal changes in cognition, behavior, or QOL in children with PHIV who take stimulants.

The primary objective of this analysis was to examine the relationship between the use of commonly prescribed stimulants and changes in measures of cognition, behavior, and QOL in children and adolescents with PHIV. We hypothesized that after adjustment for baseline levels of these measures, children with prescriptions for stimulants would show improvement in cognitive scores, parent-reported symptoms of hyperactivity and impulsivity, and indices of QOL compared to their peers with PHIV without prescriptions for stimulants.

Materials & Methods

Participants

The present study included children and adolescents with PHIV, ages 3-19 years, with and without prescriptions for stimulant medications, who were enrolled in the Pediatric AIDS Clinical Trials Group (PACTG) 219C cohort study (P219C).²²⁻²³ Exposure to stimulants was defined as having a history of prescription for at least one of the methylphenidates or amphetamine salts. Among children prescribed at least one of these stimulants, we included those who started their first stimulant after enrollment into P219C, continued that medication for at least one month, and had at least one outcome measurement obtained before (baseline measurement) and after the start of that first medication. Each participant with stimulant exposure was matched with one to three participants without stimulant exposure based on the following criteria: availability of outcome measurements, age at baseline measurement (within one year of each other), and CD4% category (< 15%, 15-25%, > 25%, or missing) within six months of baseline measurement. With three outcomes of interest (cognition, behavior, and QOL), each participant could have a maximum of three baseline measurements collected over a three-year period (see Procedures for schedules of assessment). Each potential participant without stimulant exposure was required to match the participant with stimulant exposure on age, CD4%, and availability of outcome data at all three baseline measurements.

Procedures

P219C was a longitudinal observational study of children and adolescents with PHIV exposure designed to examine long-term effects of exposure to antiretroviral (ARV) medications and complications of HIV infection. It was conducted from September 2000 to May 2007 at over 80 participating sites in the US and Puerto Rico. Informed consent and assent were obtained according to local institutional review board guidelines. Participants' medical records were abstracted at study entry and follow-up visits to obtain medical and treatment histories, including markers of immune functioning, neurologic and psychiatric diagnoses, and ARV and concomitant medications, including stimulants. Follow-up visits included standardized assessment of verbal and nonverbal cognitive abilities, parent or

primary caregiver (caregiver) report of child behavior, and reports from caregivers and older children regarding the children's QOL and current demographic and medical information. Respondents completed questionnaires independently or as interviews if they had difficulty reading. Medication start and stop dates were recorded as reported by caregivers and older participants or as documented in medical records. The baseline measure was defined as the measure completed at the visit preceding or on the same day as the visit at which the participant's first prescription was recorded. The first available outcome measure after baseline was selected as the follow-up measure.

Cognitive outcomes—Age-appropriate Wechsler scales²⁴⁻²⁹ were employed to assess verbal and nonverbal intellectual functioning. These measures were administered according to standardized procedures at baseline and every three years following enrollment. Visits were scheduled around the children's birthdays at ages 3, 6, 9, 12, and 15 years. The Wechsler tests have excellent psychometric properties and were updated as revised test versions were published. The Verbal Scale Intelligence Quotient (VIQ) and Performance Scale Intelligence Quotient (PIQ) were used in the analyses; these are age-normed standardized scores with mean (M) = 100 and standard deviation (SD) = 15. The Full Scale IQ, a summary score, was not used in order to examine potential differential effects of stimulant use on verbal and nonverbal intellectual abilities. Data were reviewed and results were excluded if considered invalid due to a child's sensory or physical impairment or insufficient proficiency in English.

Behavioral outcomes—Conners' Parent Rating Scales (CPRS-48)³⁰ were administered to caregivers at baseline and every three years until their child was 15 years old. The CPRS-48 provides measures in five behavioral domains (labeled Conduct Problem, Learning Problem, Psychosomatic, Impulsive-Hyperactive, and Anxiety) and includes a Hyperactivity Index. Age-referenced T-scores (M = 50, SD = 10) were used in the analyses. Higher scores reflected greater frequency or intensity of problem behaviors.

QOL outcomes—Standardized measures of QOL, previously validated for use with children and adolescents with PHIV,³¹ were administered to caregivers (for ages 6 months to 20 years) and study participants (ages 12-20 years) at baseline and every 6-12 months following enrollment. The General Health Perception, Health Care Utilization, and Social/School Functioning domain scores were available for all participants; the Behavior Problem Index was available for those age 5-20 years. Domain composite scores (range = 0-100) were included in the analyses. Higher scores reflected better QOL.

Statistical Analysis

Characteristics of participants with and without exposure to stimulants were compared using Fisher's exact tests, Mantel-Haenszel chi-square tests, or Pearson's chi-square tests, as appropriate. One-sample t-tests were used to determine if the average changes in outcomes during follow-up were significantly different from zero. Unadjusted and adjusted generalized estimating equation models were used to evaluate the effect of stimulant exposure and other variables on change in each of the outcomes. All adjusted models included baseline level of the outcome, child's sex, and neurologic or psychiatric diagnosis

(defined as ADHD/behavioral diagnosis, at least one other neurologic or psychiatric diagnosis, or none). Variables considered as potential confounders in the model selection process included: race/ethnicity (white non-Hispanic vs. other), HIV RNA (> 400 copies/mL vs. 400 copies/mL), Centers for Disease Control and Prevention (CDC) Class^{32,33} (Class C vs. other), caregiver (biological parent vs. other), caregiver's education (high school or greater vs. other), and type of ARV treatment (ART) used at baseline. ART was modeled as a four-category variable: highly active ART (HAART; defined as at least three drugs from at least two drug classes) with protease inhibitor (PI), HAART without PI, ART without HAART, and no ART. All covariates with $p < 0.25$ in the univariate analysis were considered for inclusion. Covariates were removed using backward selection with a significance level of $p < 0.10$. Covariates significant for at least one outcome in a given analysis (cognitive, behavioral, or QOL) were included in the multivariate model for all outcomes of that type.

Results

Participants

Of the 2,589 children with PHIV enrolled in P219C, 144 (5.6%) had a prescription for one or more stimulants (Table 1) and met inclusion criteria for this analysis. Of these, 134 (93%) had valid data for at least one of the three outcomes. Two of these participants were excluded because matching controls were unavailable. For the primary analyses, the 132 participants with prescriptions for stimulants (the prescription group [PG]) were matched with one to three participants who did not have prescriptions for stimulants (the comparison group [CG]), resulting in 392 matched controls, for a total sample of 524 participants. The analysis sets for the three outcomes were: Cognition, $n = 212$ (54 PG, 158 CG); Behavior, $n = 194$ (49 PG, 145 CG); and QOL, $n = 511$ (131 PG, 380 CG). There were 122 participants (31 PG, 91 CG) with measurements for all three outcomes.

The distribution of duration of treatment with the first-prescribed stimulant medication is shown in Table 1, overall and by stimulant group, and ranged from 1 month to 75 months. Nineteen participants switched to at least one other stimulant medication during the follow-up period.

Table 2 presents the distribution of demographic and health characteristics of all participants included in the analyses. There were significant differences between the PG and CG by gender (62% vs. 43% male). A significantly higher proportion of the PG than CG were living with biologically unrelated adults (47% vs. 28%), and their caregivers had more years of formal education than the CG (77% vs. 67% with at least high school education). Participant characteristics were similar between the total sample and the samples for each outcome measure.

Medication Class and Psychiatric or Neurologic Diagnoses

Methylphenidates were the first medications prescribed for the majority (75%) of participants with prescriptions for stimulants (Table 1). The median duration of treatment was 13.2 months (14.0 months for methylphenidates; 9.6 months for amphetamines). The

majority of the PG had one or more psychiatric or neurologic diagnoses recorded in the database (Table 2), and the prevalence of diagnoses was significantly higher than in the CG (55% vs. 28%, $p < 0.001$). A higher proportion of children in PG had a diagnosis of ADHD/other behavior disorder compared to CG (40% vs. 5%, $p < 0.001$); the groups did not differ in the prevalence of any psychiatric or neurologic diagnosis other than ADHD/other behavior disorder. There were no reported psychiatric or neurologic diagnoses for 45% of the PG. Diagnosis rates were similar between the total sample and the samples for each outcome measure.

Cognitive Outcomes

Unadjusted Wechsler mean VIQ and PIQ scores at baseline and mean changes from baseline are presented in Table 3. At baseline, mean VIQ and PIQ for both the PG and CG were in the low-average range relative to population norms, and the between-group differences were not significant. The mean retest interval for the cognitive outcomes was 31.5 months ($SD = 12.4$) and was higher for the PG (34.9 versus 30.3 months for PG and CG, respectively; $p = 0.02$). After adjustment for baseline VIQ and PIQ and other relevant covariates, having a prescription for stimulants was not associated with changes from baseline in VIQ or PIQ (Table 4).

Behavioral Outcomes

At baseline, unadjusted mean CPRS-48 scores were significantly higher in the PG than the CG on the Hyperactivity Index (61.4 vs. 50.4) and Conduct Problem (56.4 vs. 49.1), Impulsive-Hyperactive (60.7 vs. 50.0), and Learning Problem (63.0 vs. 52.8) scales (Table 3). The mean retest interval for behavioral outcomes was 26.2 months ($SD = 15.0$) and was marginally higher for the PG (29.8 vs. 25.0 months for PG and CG, respectively; $p = 0.06$). After adjusting for baseline level of the outcome and other relevant covariates, having a prescription for stimulants was significantly associated with larger average changes on the Hyperactivity Index (7.7 points) and Impulsive-Hyperactive (5.4 points) and Learning Problem (11.4 points) scales (Table 4), indicating an increase in problem behaviors, per caregiver report, from baseline to follow-up for PG as compared to CG.

QOL Outcomes

At baseline, unadjusted mean QOL scores for the PG and CG were virtually equivalent in the Health Care Utilization and Social/School Functioning domains, but the PG obtained significantly lower mean scores in the General Health Perception domain (79.4 vs. 84.8) and Behavior Problem Index (69.1 vs. 82.9) (Table 3). The mean retest interval for the QOL outcomes was 10.9 months ($SD = 7.3$) and was comparable between the two groups (11.3 vs. 10.7 months for PG and CG, respectively; $p = 0.39$). After adjustment for the baseline level of the outcome and other relevant covariates (Table 4), having a prescription for stimulants was significantly associated with decreases in the General Health Perception domain (-6.7 points) and Behavior Problem Index (-5.4 points), indicating that respondents in the PG reported changes toward poorer QOL from baseline to follow-up compared to respondents in the CG.

Discussion

We hypothesized that children with PHIV and prescriptions for stimulants, compared to those without prescriptions, would show improvements over time in cognition, behavior, and QOL. Study findings contradicted these hypotheses. After adjustment for baseline levels of the outcomes and other relevant covariates, having a prescription for stimulants was associated with worsening symptoms of hyperactivity, impulsivity, and learning problems and worsening of perceived health status in school-age children with PHIV. Participants' performance on measures of verbal and nonverbal intellectual ability, both at baseline and follow-up, was consistent with recent studies of school-age children with PHIV regardless of stimulant exposure,²⁻⁶ and there were no significant changes from baseline in VIQ or PIQ among children with PHIV, with or without prescriptions for stimulants.

At baseline, QOL domain scores assessing general health perception, behavior problems, and social/school functioning in both groups were consistent with a previous study of QOL in the P219C cohort.¹³ Compared to population norms for the CPRS-48,³⁰ the CG did not demonstrate significant behavior or learning problems, according to caregiver ratings. As expected, children in the PG demonstrated more frequent signs of hyperactivity, impulsivity, and learning problems than their peers in the general population and in the CG. The PG also showed more frequent signs of conduct problems than the CG. Findings for the PG, but not the CG, were consistent with the literature showing higher risks for behavior and learning problems among children with PHIV,^{1,2,7-9} possibly because of the relatively higher prevalence of ADHD and other behavior disorders in the PG. PHIV, per se, might not be the primary mechanism for these difficulties.^{2,34} More than half (55%) of the PG had at least one psychiatric or neurologic diagnosis recorded in the database, the majority being ADHD or another behavior disorder, yet a fairly large proportion of children in this group (45%) had no reported diagnosis. Differences in access to medical and psychiatric records¹⁷ or differences in clinical services offered across sites may have affected the availability of psychiatric and neurologic diagnoses for P219C. Thus, the present results may not accurately reflect the true frequency of psychiatric diagnoses in children with PHIV.

Children in the PG did not improve over time on measures of cognition, behavior, or QOL, consistent with an emerging literature regarding long-term efficacy of stimulant medications in the general pediatric population.^{15,16,35-37} There are plausible explanations for this finding. We have little knowledge about the synergistic relationships between stimulants, ARVs, and other medications the children may be taking. Children and adolescents with PHIV and co-morbid ADHD, compared to their uninfected peers, may require higher doses of stimulants to achieve the same therapeutic benefit because of the altered metabolism that may be associated with HIV disease and its treatments.³⁸ Stimulant treatments must be maintained to preserve initial benefits,³⁵ yet parents and older youth in the general population may use stimulants intermittently or discontinue treatment entirely for a variety of reasons, including lack of perceived benefit, medication side effects (including loss of appetite and the potential for decreased physical growth), financial costs, philosophical concerns about medicating children, and inadequate access to qualified health care professionals willing to provide medication management for ADHD.^{39,40} Family decisions over the use of stimulant treatments are further complicated by the presence of HIV

infection, a chronic illness that typically requires ongoing treatment with ARVs and frequent medical monitoring and, in addition, may put children at risk for comorbid conditions such as language disorders, learning disabilities, and behavioral or emotional disorders. It is possible that one or more of these factors influenced the findings in the present study.

This study was limited by reliance on subjective reports from caregivers without collateral reports from sources such as teachers or health care providers. For the PG, there was a lack of information concerning stimulant dosing and medication adherence. For example, children in the PG may have performed more poorly than those in the CG because they were not adherent to their stimulant treatment regimens, a possibility consistent with recent literature on medical treatment of children and adults with ADHD.⁴¹ Follow-up intervals were linked to children's ages and dates of enrollment into P219C, not to medication start and stop dates, and there was wide variability in treatment duration, with some participants continuing their first prescription for as little as one month. Such variability limits the interpretation of study findings. Children who entered P219C with prescriptions for stimulants were not included in the study, limiting the generalizability of the findings. Information was lacking concerning important life events during the lengthy retest intervals as well as non-medical therapies that may have been provided to families, for example, behavior therapy, parent training, and general educational and psychosocial supports. The imbalance in some covariates and lack of data on potentially important confounding variables suggests that the use of an alternative research design, such as propensity score matching, should be explored in future studies. Although the age range was wide, and analyses were not stratified by age, the outcome measures were standardized and appropriate for use with children and adolescents across the age range included in the study.

To our knowledge, this study is one of the first to examine the association of stimulant prescription use with changes in important indicators of well-being in children and adolescents with PHIV. Despite its limitations, the results of the study are intriguing and support a growing consensus⁴²⁻⁴⁵ that expectations of parents, teachers, and medical providers may not be well aligned with the long-term effects of these medications on children's behavior, academics, and QOL. This study provides preliminary, exploratory data concerning the associations between stimulant prescription use and the selected outcomes. It is important to pursue this research to gain a fuller understanding of the most appropriate, evidence-informed treatments for children with PHIV and symptoms of ADHD and other behavior disorders.

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Appendix

Participating institutions in the US-based multisite cohort study, PACTG 219/219C, between 1993-2004

The following institutions and clinical site investigators participated in PACTG 219/219C: University of New Jersey Medical and Dental School - Department of Pediatrics, Division of Allergy, Immunology & Infectious Diseases: *Dr. Arlene Bardeguez, Dr. Arry Dieudonne, Linda Bettica, Juliette Johnson*, Boston Medical Center, Division of Pediatric Infectious Diseases: *Dr. Stephen I. Pelton, Dr. Ellen R. Cooper, Lauren Kay, Ann Marie Regan*, Med, Children's Hospital LA - Department of Pediatrics, Division of Clinical Immunology & Allergy: *Dr. Joseph A. Church, Theresa Dunaway*, Long Beach Memorial Medical Center, Miller Children's Hospital: *Dr. Audra Deveikis, Dr. Jagmohan Batra, Susan Marks, Ilaisanee Fineanganofa*, Harbor - UCLA Medical Center - Department of Pediatrics, Division of Infectious Diseases: *Dr. Margaret A. Keller, Dr. Nasser Redjal, Spring Wettgen, Sheryl Sullivan*, Johns Hopkins Hospital & Health System - Department of Pediatrics, Division of Infectious Diseases: *Dr. Nancy Hutton, Beth Griffith, Mary Joyner, Carolyn Keifer*, University of Maryland Medical Center, Division of Pediatric Immunology & Rheumatology: *Dr. Douglas Watson, Dr. John Farley*, Texas Children's Hospital, Allergy & Immunology Clinic: *Dr. Mary E. Paul, Chivon D. Jackson, Faith Minglana, Dr. Heidi Schwarzwald*, Cook County Hospital: *Dr. Kenneth M. Boyer, Dr. Jamie Martinez, Dr. James B. McAuley, Maureen Haak*, Children's Hospital of Columbus, Ohio: *Dr. Michael Brady, Dr. Katalin Koranyi, Jane Hunkler, Charon Callaway*, University of Miami Miller School of Medicine, Division of Pediatric Immunology & Infectious Disease: *Dr. Gwendolyn B. Scott, Dr. Charles D. Mitchell, Dr. Claudia Florez, Joan Gamber*, University of California San Francisco School of Medicine, Department of Pediatrics: *Dr. Diane W.*

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Table 1
Duration of Treatment with First Prescribed Stimulant Medication by Stimulant Group

	N	Stimulant Group		Total
		Methylphenidates ^a	Amphetamines ^b	
Duration of treatment (months)		102	30	132
	Median (Q1,Q3)	14.0 (3.7, 31.5)	9.6 (2.5, 38.9)	13.2 (3.3, 32.0)
	Min, Max	1.1, 75.0	1.0, 58.0	1.0, 75.0

^aBrand names included Concerta (Janssen Pharmaceuticals Inc., Titusville, NJ), Daytrana (Noven Pharmaceuticals Inc., Miami, FL), Focalin, Focalin XR, Ritalin, Ritalin LA, Ritalin SR (Novartis Corporation, New York, NY), Methylin (Shionogi Inc., Florham Park, NJ), Methylin ER (Mallinckrodt Pharmaceuticals, St. Louis, MO), Metadate CD, and Metadate ER (UCB Pharma, Anderlecht, Belgium).

^bBrand names included Adderall, Adderall XR, Dextrostat, Vyvanse (Shire US Inc., Florence, KY), and Dexedrine (GlaxoSmithKline, Hanover, PA).

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Table 2
Demographic and Health Characteristics of Study Participants^a by Group

Characteristic		Group		p-value
		Comparison (n = 392)	Prescription (n = 132)	
Age at baseline	3 to 6 years	71 (18%)	24 (18%)	0.59 ^b
	> 6 to 9 years	159 (41%)	61 (46%)	
	> 9 to 12 years	105 (27%)	27 (20%)	
	> 12 to 16 years	57 (15%)	20 (15%)	
Sex	Male	168 (43%)	82 (62%)	< 0.001 ^c
	Female	224 (57%)	50 (38%)	
Race/ethnicity	Black, non-Hispanic	251 (64%)	77 (58%)	0.56 ^e
	Hispanic (regardless of race)	74 (19%)	31 (23%)	
	White, non-Hispanic	58 (15%)	22 (17%)	
	Other	9 (2%)	2 (2%)	
CD4%	Missing	12 (3%)	4 (3%)	0.88 ^b
	0 - < 15	19 (5%)	7 (5%)	
	15 - 25	82 (21%)	28 (21%)	
	> 25	279 (71%)	93 (70%)	
HIV RNA (copies/mL)	0 - 400	193 (51%)	67 (52%)	0.58 ^b
	401 - 10,000	111 (29%)	39 (30%)	
	> 10,000	76 (20%)	22 (17%)	
CDC class C	AIDS-defining illness	87 (24%)	29 (24%)	1.00 ^c
ARV use at baseline	HAART with PI	262 (67%)	103 (78%)	0.10 ^e
	HAART without PI	34 (9%)	6 (5%)	
	Other ARV regimen	79 (20%)	19 (14%)	
	No ART	17 (4%)	4 (3%)	
Caregiver	Biological parent	186 (47%)	35 (27%)	< 0.001 ^e
	Relative	95 (24%)	35 (27%)	
	Other adult, shelter, home, or other	111 (28%)	62 (47%)	
Caregiver education	Grade 1 - 11	91 (23%)	16 (12%)	0.02 ^e
	High school diploma	113 (29%)	44 (33%)	
	Some college or technical school	101 (26%)	31 (23%)	
	College graduate or higher	48 (12%)	28 (21%)	
	Other/Unknown	39 (10%)	13 (10%)	
Psychiatric or neurologic diagnosis ^d	ADHD/other behavior disorder	19 (5%)	53 (40%)	< 0.001 ^e
	At least one other disorder ^f	91 (23%)	20 (15%)	
	None	282 (72%)	59 (45%)	
Transition between Wechsler test versions ^g	No	73 (46%)	30 (56%)	0.27 ^c
	Yes	85 (54%)	24 (44%)	

Characteristic		Group		p-value
		Comparison (n = 392)	Prescription (n = 132)	
Transition between QOL versions ^h	No	345 (91%)	124 (95%)	0.20 ^c
	Yes	35 (9%)	7 (5%)	

^aTotal sample (N = 524), including all participants with Wechsler, CPRS-48, or QOL data, unless otherwise specified.

^bMantel-Haenszel Chi-Square.

^cFisher's Exact Test.

^dIncludes diagnoses recorded until the time of follow-up.

^eChi-Square Test.

^fOther disorders included intellectual disability/developmental disorder, depression/anxiety/bipolar disorder (including dysthymia and suicidal tendencies), encephalopathy/cerebral palsy, hypotonia/hypertonia, epilepsy/seizure/infantile spasm, and microcephaly/failure to thrive.

^gIncludes participants with Wechsler data only.

^hIncludes participants with QOL data only.

Table 3
Unadjusted Scores at Baseline and Change from Baseline by Outcome Measure for Participants With (PG) and Without (CG) Prescriptions for Stimulant Medications

Measure	Baseline			Change from Baseline ^b		
	Comparison Group (CG) Mean (SD), n	Prescription Group (PG) Mean (SD), n	Between-group comparison (p-value) ^d	Comparison Group (CG) Mean (SD), n	Prescription Group (PG) Mean (SD), n	Between-group comparison (p-value) ^d
Wechsler IQ Scores						
Verbal Scale (VIQ)	85.7 (15.6), 158	83.3 (15.7), 54	0.33	-0.2 (9.4), 158	2.5 (11.0), 54	0.10
Performance Scale (PIQ)	88.9 (17.2), 158	88.1 (14.5), 54	0.77	-0.9 (9.8), 158	2.8 (10.8), 54	0.03
CPRS-48 Scale Scores						
Anxiety	48.7 (8.1), 145	50.9 (12.2), 49	0.25	0.2 (8.7), 145	-2.0 (15.0), 49	0.29
Conduct Problem	49.1 (12.0), 145	56.4 (17.2), 49	0.003	-1.2 (11.4), 145	-2.5 (15.8), 49	0.58
Hyperactivity Index	50.4 (13.4), 145	61.4 (16.8), 49	<0.001	-0.9 (12.4), 145	1.4 (17.9), 49	0.36
Impulsive-Hyperactive	50.0 (12.0), 145	60.7 (14.3), 49	<0.001	-1.4 (11.7), 145	-1.6 (16.3), 49	0.94
Learning Problem	52.8 (15.4), 145	63.0 (16.9), 49	<0.001	0.2 (13.5), 145	4.7 (19.8), 49	0.12
Psychosomatic	54.3 (14.6), 145	54.7 (15.8), 49	0.88	0.3 (14.8), 145	0.4 (18.8), 49	0.97
QOL Domain Scores						
General Health Perception	84.8 (16.0), 378	79.4 (17.4), 131	0.002	1.4 (19.0), 378	-0.8 (22.0), 131	0.31
Health Care Utilization	95.4 (6.9), 380	95.0 (6.2), 131	0.56	0.4 (8.3), 380	0.4 (8.0), 131	0.91
Social/School Functioning	90.2 (11.5), 377	90.3 (12.1), 130	0.97	-0.4 (12.9), 377	0.2 (11.3), 130	0.59
Behavior Problems Index	82.9 (13.6), 357	69.1 (21.6), 124	<0.001	0.6 (12.5), 357	0.3 (17.8), 124	0.88

^aEstimated using unadjusted generalized estimating equation models.

^bMean changes from baseline in Wechsler IQ scores, CPRS-48 scale scores, and QOL domain scores were not significantly different from zero in either the Prescription or Comparison groups, using one-sample t-tests.

Table 4
Estimated Effect of Stimulant Prescription Use on Change from Baseline in Cognitive, Behavioral, and Quality of Life Outcomes after Adjustment for Relevant Covariates

Measure	Retest Interval (Mean, months)	Outcome	Estimated Effect of Stimulant Prescription Use	p-value
Wechsler Score ^a	31.0	Verbal Scale IQ (VIQ)	0.9	0.60
		Performance Scale IQ (PIQ)	1.6	0.37
CPRS-48 Scale ^b	26.1	Anxiety	-0.8	0.62
		Conduct Problem	2.1	0.37
		Hyperactivity Index	7.7	0.01
		Impulsive-Hyperactive	5.4	0.04
		Learning Problem	11.4	< 0.001
		Psychosomatic	2.1	0.43
		QOL Domain ^c	11.1	General Health Perception
Health Care Utilization	-0.2	0.82		
Social/School Functioning	0.6	0.63		
Behavior Problem Index	-5.4	0.01		

^a Adjusted for baseline level of measure, sex, psychiatric or neurologic diagnosis (ADHD/other behavior disorder, at least one other disorder, or none), race (white, non-Hispanic vs. other), CDC class (C vs. other), and caregiver (biological parent vs. other).

^b Adjusted for baseline level of measure, sex, psychiatric or neurologic diagnosis, and caregiver.

^c Adjusted for baseline level of measure, sex, psychiatric or neurologic diagnosis, race, HIV RNA (detectable vs. undetectable), caregiver education (high school diploma or higher vs. other), and transition between QOL versions (Social/School Functioning domain and Behavior Problem Index only).