SUPPLEMENT 1

Measures

The Nisonger Child Behavior Rating Form (NCBRF) was used to determine eligibility and clinical improvement as well as one of the primary outcome measures. The Nisonger Child Behavior Rating Form (NCBRF)-Typical IQ provides one prosocial subscale (Positive/Social) and six problem behavior subscales: (a) Conduct Problem, (b) Oppositional Behavior, (c) Hyperactive, (d) Inattentive, (e) Overly Sensitive, and (f) Withdrawn/Dysphoric. The NCBRF has excellent internal consistency, distinguishes between controls and patients with disruptive behavior disorders (DBDs), and its predecessor (for children with developmental disabilities) was highly drug-sensitive. Conduct Problem and Oppositional Behavior map closely to *DSM-IV-TR* symptoms of conduct disorder (CD) and oppositional defiant disorder (ODD); they were scored together to form a variable called the Disruptive-Total (D-Total). The D-Total was the primary outcome measure for this study. The Hyperactive and Inattentive subscale scores were combined to form an ADHD-Total. To be eligible for the study, a child had to obtain a parent-rated NCBRF D-Total score of ≥ 27 (90^{th} percentile). During the acute trial, a "clinical responder" was defined in part as having a parent-rated NCBRF D-Total score of $\leq$15 (within 0.5 of the normative mean). For the purposes of statistical evaluation at study endpoint, a clinical responder was defined in part as having a reduction to the NCBRF D-Total of $\geq$25%.

Clinicians completed the Overt Aggression Scale-Modified (OAS–M), a seven-item instrument from both parent and child report. Questions assess aggression on the dimensions of assaults against (a) objects, (b) others, and (c) self, on rating subscales ranging from 0 (no events) to 5 (severe events). Children receiving a score of at least 3, both at screen and at baseline, qualified for inclusion. Providing some notion of initial severity, a score of 3 for assaults against objects is anchored with "Breaks objects, smashes windows," whereas a score of 3 for assaults against others is characterized as "Attacks others, causing mild injury (bruises, sprains, welts, etc.)."

In order to qualify, a child also required a Clinical Global Impressions–Severity (CGI-S) score of at least 4, moderately ill, reflecting the presence of consistent attention-deficit/hyperactivity disorder (ADHD), disruptive, and physically aggressive/destructive behavior. Anger, defiance, and aggressive speech were not enough to qualify children for the study. Participants had to display behavior that was physically harmful to others, themselves, or the environment around them. We established interrater reliability on the CGI-S by discussion at investigators meetings, subsequent "gold standard" test vignettes, and repeated re-certifications of blinded evaluators.

During the acute trial, a "clinical responder" was defined in part as having a blinded-evaluator-determined Clinical Global Impressions–Improvement (CGI-I) score of 1 (very much improved). We established interrater reliability on the CGI-I subscales by discussion at investigators meetings, subsequent

"gold standard" test vignettes, and repeated re-certifications of blinded evaluators. For the purposes of statistical evaluation at study endpoint, a clinical responder was defined in the more usual way, a CGI-I of 1 (very much improved) or 2 (much improved).

The Child and Adolescent Symptom Inventory–4R (CASI-4R) assesses a broad range of *DSM-IV*-defined disorders and was administered at initial diagnostic evaluation (parents only), baseline, and Week 9. Individual items are rated on a scale from 0 (never) to 3 (very often). The last item in each CASI-4R symptom scale assesses impairment: "How often do the behaviors in [this symptom category] interfere with youth's ability to do schoolwork or get along with others?" For the ADHD subscale, there is one impairment item for all subtypes. Impairment severity is rated on a 4-point scale, and the impairment cutoff score (categorical) is a frequency rating of often or very often.

Parents completed the Antisocial Behavior Scale (ABS), a 28-item rating scale that has an Instrumental (Proactive) Aggression subscale (5 proactive items and 5 covert antisocial items) and a Reactive Aggression subscale (6 items). This instrument was used to differentiate affective and instrumental subtypes of aggression and to assess treatment effects on both.

Extrapyramidal symptoms were assessed with the Barnes Akathisia Scale and Abnormal Involuntary Movement Scale (AIMS). The Barnes Akathisia Scale is a clinician-completed scale utilizing both objective observation/clinical judgment and the patient's subjective experience of restlessness. The Simpson-Angus Rating Scale checks for extrapyramidal side effects (rigidity, dystonia, and abnormal glabellar reflex) of antipsychotics, a standardized clinician-rated review of tremor, dyskinesia, and other possible antipsychotic neuromotor side effects.

Laboratory measures included weight, body mass index (BMI) percentiles, heart rate, blood pressure, and prolactin concentrations.

Table S1: Baseline Characteristics of Children Lost to Follow-Up Versus Week 52 Participants

Characteristic	Lost to Follow-Up (*n*=60)	Week 52 Participants (*n*=108)
Gender, n (%)		
Male	46 (76.7)	83 (76.9)
Female	14 (23.3)	25 (23.1)
Disorder, n (%)		
Conduct disorder	16 (26.7)	28 (25.9)
Oppositional defiant disorder	44 (73.3)	80 (74.1)
Age (y) at screening, m (SD)	9.0 (2.1)	8.8 (2.0)
IQ at screening, m (SD)	93.8 (13.5)	98.9 (14.2)
Race, n (%)		
White	28 (46.7)	61 (56.5)
Black	26 (43.3)	32 (29.6)
Asian	0 (0.0)	1 (0.9)
American Indian or Alaskan Native	1 (1.7)	1 (0.9)
Multiracial	4 (6.8)	13 (12.0)
Ethnicity, n (%)		
Hispanic origin	4 (6.7)	5 (4.6)
Non-Hispanic origin	55 (91.7)	102 (94.4)
Unknown	1 (1.7)	1 (0.9)
Child's type of school, n (%)		
Other	10 (16.7)	13 (12.0)
Regular public (or parochial)	50 (83.3)	95 (88.0)
Mother's employment, n (%)		
Keeping house	4 (6.7)	17 (15.7)
Other	27 (45.0)	32 (29.6)
Working full-/part-time	29 (48.3)	59 (54.6)
Father's employment, n (%)		
Keeping house	1 (1.7)	0 (0.0)
Other	30 (50.0)	45 (41.7)
Working full-/part-time	27 (45.0)	62 (57.4)
Unknown	2 (3.3)	1 (0.9)

Mother's education, n (%)		
Some high school or less	10 (16.7)	6 (5.6)
High school graduate or GED	14 (23.3)	26 (24.1)
Some college or more	36 (60.0)	75 (69.4)
Not in household or unknown	0 (0.0)	1 (0.9)
Father's education, n (%)		
Some high school or less	4 (6.7)	3 (2.8)
High school graduate or GED	21 (35.0)	28 (25.9)
Some college or more	14 (23.3)	45 (41.7)
Not in household or unknown	21 (35.0)	32 (29.6)
Income, n (%)		
Less than $20,000	25 (41.7)	36 (33.3)
$20,001-$40,000	15 (25.0)	20 (18.5)
$40,001-$60,000	10 (16.7)	14 (13.0)
$60,001-$90,000	5 (8.3)	16 (14.8)
More than $90,000	4 (6.7)	17 (15.7)
Unknown	1 (1.7)	5 (4.6)
NCBRF, D-Total, mean (SD)	44.4 (10.7)	45.8 (10.9)
CGI-S, n (%)		
4	10 (16.7)	12 (11.1)
5	36 (60.0)	71 (65.7)
6	14 (23.3)	25 (23.1)
OAS (parent-rated),[a] n (%)		
Assault against objects	48 (80.0)	82 (75.9)
Assault against others	53 (88.3)	102 (94.4)
Assault against self	5 (8.3)	9 (8.3)

Note: No statistically significant differences between those that participated in the follow-up vs. those that did not except for IQ (two-sample *t*-test, p=.023). CGI = Clinical Global Impressions; GED = general educational development; NCBRF = Nisonger Child Behavior Rating Form; OAS-M = Overt Aggression Scale–Modified.
[a]Number and percent for those with scores of 3 or higher.

Table S2: Primary and Secondary Behavioral Outcomes Based on Randomized Treatment Status

Outcome Measure	Baseline	Week 52	*p* Values	
			Trt*visit interaction[a]	Week 52[b]
Basic, n	55	55		
Augmented, n	53[e]	52		
NCBRF Measures				
D-Total				
Basic	44.6 (10.3)	24.9 (16.9)	0.0811	0.028[b]
Augmented	42.6 (10.7)	18.3 (12.3)		
Positive Social				
Basic	8.3 (3.9)	15.3 (6.3)	0.9138	0.1734
Augmented	9.8 (3.4)	16.6 (5.8)		
Overly Sensitive				
Basic	6.5 (3.3)	4.1 (3.1)	0.4738	0.1403
Augmented	6.1 (3.2)	3.2 (2.8)		
ADHD				
Basic	25.5 (6.1)	13.5 (8.3)	0.1707	0.1956
Augmented	25.7 (5.4)	11.6 (7.2)		
Withdrawn-dysphoric				
Basic	13.9 (8.6)	8.6 (8.3)	0.2130[c]	0.1731[c]
Augmented	13.6 (8.3)	6.6 (6.8)		
ABS Measures				
Proactive				
Basic	20.3 (5.1)	16.7 (5.1)	0.0881	0.0249
Augmented	19.8 (4.6)	14.9 (3.9)		
Reactive				
Basic	16.1 (1.8)	13.0 (3.1)	0.9304	0.1183
Augmented	15.3 (2.6)	12.2 (2.8)		
CASI – mean item score				
ADHD				
Basic	2.39 (0.55)	1.33 (0.67)	0.6468	0.0923
Augmented	2.27 (0.54)	1.15 (0.59)		
Attention				

Basic	2.46 (0.60)	1.45 (0.67)	0.7965	0.0409
Augmented	2.25 (0.60)	1.21 (0.71)		
Hyperactivity-Impulsivity				
Basic	2.31 (0.67)	1.20 (0.76)	0.5551	0.3109
Augmented	2.29 (0.68)	1.09 (0.65)		
Hyperactivity				
Basic	2.33 (0.74)	1.09 (0.87)	0.4131	0.3501
Augmented	2.36 (0.68)	0.98 (0.64)		
Impulsivity				
Basic	2.29 (0.73)	1.33 (0.78)	0.8104	0.3615
Augmented	2.21 (0.84)	1.22 (0.81)		
ODD				
Basic	2.42 (0.52)	1.44 (0.82)	0.4255	0.0598
Augmented	2.29 (0.64)	1.19 (0.66)		
Anger Irritability Symptoms				
Basic	2.34 (0.60)	1.42 (0.91)	0.584	0.0981
Augmented	2.20 (0.75)	1.18 (0.69)		
Noncompliance				
Basic	2.47 (0.57)	1.45 (0.81)	0.3508	0.06
Augmented	2.34 (0.63)	1.20 (0.72)		
Conduct Disorder				
Basic	0.58 (0.42)	0.27 (0.30)	0.3013[c]	0.0382[c]
Augmented	0.50 (0.45)	0.17 (0.22)		
Peer Conflict Scale				
Basic	1.59 (0.95)	0.83 (0.81)	0.1908[c]	0.1682[c]
Augmented	1.50 (0.86)	0.58 (0.62)		
Physical Aggression				
Basic	1.66 (0.99)	0.85 (0.85)	0.2115[c]	0.1722[c]
Augmented	1.59 (0.93)	0.61 (0.66)		
Nonphysical Aggression				
Basic	1.60 (1.07)	0.92 (0.90)	0.0523[c]	0.1404[c]
Augmented	1.56 (0.93)	0.64 (0.72)		
Object Aggression				

Basic	1.45 (1.07)	0.63 (0.84)	0.5951[c]	0.1356[c]
Augmented	1.22 (0.96)	0.40 (0.69)		
Generalized Anxiety				
Basic	1.17 (0.63)	0.64 (0.54)	0.5475[c]	0.6842[c]
Augmented	1.05 (0.64)	0.60 (0.53)		
Other Anxiety				
Basic	0.42 (0.43)	0.29 (0.36)	0.5828[c]	0.4920[c]
Augmented	0.43 (0.50)	0.27 (0.37)		
Social Phobia				
Basic	0.52 (0.76)	0.40 (0.60)	0.4166[c]	0.1820[c]
Augmented	0.27 (0.43)	0.29 (0.56)		
Separation Anxiety				
Basic	0.54 (0.77)	0.31 (0.52)	0.6816[c]	0.1106[c]
Augmented	0.37 (0.50)	0.20 (0.32)		
Schizoid Personality Disorder				
Basic	0.48 (0.62)	0.45 (0.59)	0.4163[c]	0.7404[c]
Augmented	0.67 (0.82)	0.46 (0.71)		
Enuresis, Encopresis				
Basic	0.29 (0.54)	0.19 (0.38)	0.2522[c]	0.3375[c]
Augmented	0.57 (0.83)	0.32 (0.58)		
Schizophrenia				
Basic	0.31 (0.41)	0.16 (0.34)	0.7481[c]	0.3451[c]
Augmented	0.25 (0.40)	0.12 (0.27)		
Depression				
Basic	0.36 (0.28)	0.20 (0.22)	0.6795[c]	0.2104[c]
Augmented	0.32 (0.32)	0.20 (0.31)		
Manic Symptoms				
Basic	1.05 (0.79)	0.48 (0.59)	0.4577[c]	0.1239[c]
Augmented	0.79 (0.74)	0.36 (0.44)		
Autism Spectrum				
Basic	0.73 (0.55)	0.36 (0.42)	0.9621[c]	0.4682[c]
Augmented	0.69 (0.54)	0.30 (0.41)		
Anorexia				

Basic	0.28 (0.40)	0.16 (0.31)	0.0160[c]	0.2955[c]
Augmented	0.17 (0.34)	0.21 (0.31)		
Bulimia Nervosa				
Basic	0.28 (0.47)	0.14 (0.26)	0.7424[c]	0.6344[c]
Augmented	0.27 (0.44)	0.18 (0.35)		
Anxiety Composite				
Basic	0.67 (0.42)	0.42 (0.40)	0.6580[c]	0.6270[c]
Augmented	0.60 (0.46)	0.38 (0.39)		
Schizophrenia Spectrum Disorder				
Basic	0.37 (0.40)	0.26 (0.36)	0.7294[c]	0.3639[c]
Augmented	0.39 (0.48)	0.24 (0.38)		
CASI – I, % impaired[d]				
ADHD				
Basic	51 (92.7%)	21 (38.2%)	0.4138	0.7571
Augmented	44 (86.3%)	19 (36.5%)		
ODD				
Basic	49 (89.1%)	18 (33.3%)	0.3852	0.8758
Augmented	41 (80.4%)	16 (31.4%)		
Conduct Disorder				
Basic	20 (36.4%)	7 (12.7%)	0.2079	0.0673
Augmented	14 (26.4%)	1 (1.9%)		
Peer Conflict Scale				
Basic	20 (46.5%)	7 (15.9%)	0.1476	0.2198
Augmented	21 (55.3%)	3 (7.9%)		
Generalized Anxiety				
Basic	23 (41.8%)	8 (14.5%)	0.4122	0.1543
Augmented	18 (34.0%)	3 (5.8%)		
Social Phobia				
Basic	8 (14.5%)	3 (5.5%)	0.078	0.7112
Augmented	2 (3.8%)	4 (7.8%)		
Separation Anxiety				
Basic	9 (16.4%)	3 (5.5%)	0.3859	0.3549
Augmented	1 (1.9%)	1 (1.9%)		

Schizoid Personality Disorder				
Basic	5 (9.1%)	2 (3.6%)	0.6343	0.6533
Augmented	11 (21.2%)	3 (5.8%)		
Schizophrenia				
Basic	3 (5.5%)	2 (3.6%)	0.8132	0.9391
Augmented	4 (7.5%)	2 (3.8%)		
Depression				
Basic	6 (10.9%)	2 (3.6%)	0.4975	0.4905
Augmented	6 (11.3%)	4 (7.7%)		
Manic Symptoms				
Basic	18 (32.7%)	4 (7.3%)	0.5754	0.9978
Augmented	13 (24.5%)	4 (7.7%)		
Autism Spectrum				
Basic	14 (25.5%)	4 (7.3%)	0.9845	0.9267
Augmented	15 (28.3%)	4 (7.7%)		
Anorexia				
Basic	1 (1.8%)	1 (1.8%)	0.9964	0.8443
Augmented	2 (3.8%)	2 (3.8%)		
Bulimia Nervosa				
Basic	2 (3.6%)	0 (0.0%)	0.9964	0.9955
Augmented	1 (1.9%)	0 (0.0%)		
CGI-I, % much/very much improved				
Basic	1 (1.8%)	33 (60%)	0.7163	0.1445
Augmented	1 (1.9%)	38 (73.1%)		
CGI-S, % non-clinical				
Basic	0 (0%)	23 (41.8%)	n/a	0.0200[f]
Augmented	0 (0%)	34 (65.4%)		

Note: ABS = Antisocial Behavior Scale; ADHD = attention-deficit/hyperactivity disorder; CASI = Child and Adolescent Symptom Inventory; CD = conduct disorder; CGI = Clinical Global Impressions; I = impairment; NCBRF = Nisonger Child Behavior Rating Form; ODD = oppositional defiant disorder; S = severity.

[a] A significant Trt*Visit interaction signifies that the change from baseline to Week 52 significantly differed for the Basic and Augmented treatment strategies.

[b] Difference between groups at Week 52, determined by mixed model simple main effects test.

[c] Square root transformation.

[d] Impairment defined as often or very often.

[e] At baseline, Augmented *n*=51 for ADHD and ODD scales.

[f] Fisher's exact test, Week 52 data.

Table S3: Behavioral Outcomes for Children Receiving Consistent Treatment From Acute Trial to Follow-Up

Outcome Measure	Baseline Mean (SD)	Week 52 Mean (SD)	*p* Values	
			Trt*visit interaction[a]	Week 52[b]
NCBRF Measures				
D-Total				
Basic	44.2 (11.2)	23.3 (16.5)	0.2896	0.0582
Augmented	40.6 (9.9)	15.3 (9.9)		
Positive Social				
Basic	8.7 (4.3)	15.0 (6.1)	0.0777	0.0047
Augmented	10.4 (3.2)	19.7 (4.4)		
Overly Sensitive				
Basic	6.2 (3.6)	4.7 (2.9)	0.2223	0.0964
Augmented	6.2 (3.2)	3.3 (2.5)		
ADHD				
Basic	24.5 (6.2)	12.5 (8.6)	0.0182	0.1571
Augmented	26.5 (5.1)	9.2 (6.5)		
Withdrawn-dysphoric				
Basic	12.1 (8.8)	8.9 (8.5)	0.1937[c]	0.3229[c]
Augmented	13.1 (8.2)	5.5 (4.6)		
ABS Measures				
Proactive				
Basic	21.2 (4.5)	17.1 (4.6)	0.3400	0.0156
Augmented	19.2 (4.5)	14.0 (3.5)		
Reactive				
Basic	16.0 (1.8)	13.0 (3.5)	0.2824	0.1597
Augmented	15.8 (2.4)	11.7 (2.4)		
CASI – Mean Item Score Measures				
ADHD				
Basic	2.38 (0.51)	1.26 (0.71)	0.1614	0.1022
Augmented	2.35 (0.50)	0.94 (0.55)		
ODD				

Basic	2.53 (0.51)	1.36 (0.78)	0.7410	0.0558
Augmented	2.22 (0.65)	0.98 (0.49)		
Conduct Disorder				
Basic	0.54 (0.43)	0.25 (0.31)	0.0685[c]	0.0238[c]
Augmented	0.45 (0.38)	0.10 (0.13)		
Peer Conflict Scale				
Basic	1.60 (0.85)	0.83 (0.76)	0.2431[c]	0.0610[c]
Augmented	1.29 (0.86)	0.42 (0.43)		
Generalized Anxiety				
Basic	1.06 (0.61)	0.58 (0.55)	0.3612[c]	0.6692[c]
Augmented	1.15 (0.59)	0.46 (0.35)		
Other Anxiety				
Basic	0.42 (0.43)	0.28 (0.35)	0.0414[c]	0.0749[c]
Augmented	0.41 (0.40)	0.16 (0.26)		
Social Phobia				
Basic	0.35 (0.71)	0.35 (0.63)	0.1449[c]	0.0944[c]
Augmented	0.23 (0.32)	0.07 (0.17)		
Separation Anxiety				
Basic	0.36 (0.66)	0.21 (0.47)	0.7210[c]	0.9982[c]
Augmented	0.33 (0.45)	0.17 (0.27)		
Schizoid Personality Disorder				
Basic	0.43 (0.63)	0.32 (0.44)	0.3680[c]	0.9701[c]
Augmented	0.61 (0.73)	0.25 (0.27)		
Enuresis, Encopresis				
Basic	0.40 (0.66)	0.28 (0.44)	0.7031[c]	0.1893[c]
Augmented	0.28 (0.54)	0.15 (0.44)		
Schizophrenia				
Basic	0.27 (0.35)	0.13 (0.24)	0.2436[c]	0.0344[c]
Augmented	0.17 (0.20)	0.04 (0.10)		
Depression				
Basic	0.34 (0.31)	0.23 (0.28)	0.0892[c]	0.0389[c]

Augmented	0.25 (0.22)	0.09 (0.14)		
Manic Symptoms				
Basic	0.71 (0.63)	0.33 (0.40)	0.2586[c]	0.0950[c]
Augmented	0.71 (0.78)	0.15 (0.24)		
Autism Spectrum				
Basic	0.65 (0.47)	0.38 (0.41)	0.2266[c]	0.1798[c]
Augmented	0.66 (0.44)	0.18 (0.21)		
Anorexia				
Basic	0.19 (0.33)	0.21 (0.38)	0.8071[c]	0.7516[c]
Augmented	0.21 (0.37)	0.15 (0.24)		
Bulimia Nervosa				
Basic	0.20 (0.46)	0.15 (0.29)	0.7011[c]	0.6768[c]
Augmented	0.24 (0.38)	0.20 (0.35)		
Anxiety Composite				
Basic	0.61 (0.43)	0.39 (0.42)	0.1080[c]	0.2580[c]
Augmented	0.62 (0.34)	0.24 (0.24)		
Schizophrenia Spectrum Disorder				
Basic	0.32 (0.41)	0.19 (0.23)	0.1991[c]	0.3033[c]
Augmented	0.32 (0.28)	0.11 (0.14)		
CASI–Impairment, % impaired[d]				
ADHD				
Basic	19 (95.0%)	5 (25.0%)	0.6638	0.9456
Augmented	21 (91.3%)	6 (26.1%)		
ODD				
Basic	18 (90.0%)	4 (21.1%)	0.4062	0.9198
Augmented	18 (78.3%)	5 (22.7%)		
Conduct Disorder				
Basic	5 (25.0%)	3 (15.0%)	0.5943	0.5774
Augmented	5 (21.7%)	0 (0.0%)		
Peer Conflict Scale				
Basic	10 (62.5%)	4 (23.5%)	0.9968	0.9965

Augmented	7 (43.8%)	0 (0.0%)		
Generalized Anxiety				
Basic	5 (25.0%)	3 (15.0%)	0.9884	0.9887
Augmented	7 (30.4%)	0 (0.0%)		
Social Phobia				
Basic	3 (15.0%)	1 (5.0%)	0.7716	0.6827
Augmented	1 (4.3%)	0 (0.0%)		
Separation Anxiety				
Basic	2 (10.0%)	1 (5.0%)	0.9935	0.9923
Augmented	1 (4.3%)	0 (0.0%)		
Schizoid Personality Disorder				
Basic	2 (10.0%)	0 (0.0%)	N/A	N/A
Augmented	4 (17.4%)	0 (0.0%)		
Schizophrenia				
Basic	0 (0.0%)	0 (0.0%)	N/A	N/A
Augmented	0 (0.0%)	0 (0.0%)		
Depression				
Basic	2 (10.0%)	1 (5.0%)	0.4108	0.6417
Augmented	1 (4.3%)	2 (8.7%)		
Manic Symptoms				
Basic	5 (25.0%)	0 (0.0%)	0.9952	0.9953
Augmented	5 (21.7%)	1 (4.3%)		
Autism Spectrum				
Basic	6 (30.0%)	2 (10.0%)	0.9966	0.9966
Augmented	6 (26.1%)	0 (0.0%)		
Anorexia				
Basic	0 (0.0%)	1 (5.0%)	0.9968	0.9579
Augmented	1 (4.3%)	0 (0.0%)		
Bulimia Nervosa				
Basic	0 (0.0%)	0 (0.0%)	0.9997	0.9998
Augmented	0 (0.0%)	0 (0.0%)		

CGI-I, % much/very much improved				
Basic	0 (0.0%)	13 (65.0%)	0.9605	0.0932
Augmented	1 (4.4%)	20 (87.0%)		
CGI-S, % non-clinical				
Basic	0 (0.0%)	11 (55.0%)	n/a	0.0943[e]
Augmented	0 (0.0%)	19 (82.6%)		

Note: ABS = Antisocial Behavior Scale; ADHD = attention-deficit/hyperactivity disorder; CASI = Child and Adolescent Symptom Inventory; CD = conduct disorder; CGI = Clinical Global Impressions; I = impairment; NCBRF = Nisonger Child Behavior Rating Form; ODD = oppositional defiant disorder; S = severity.

[a] A significant Trt*Visit interaction signifies that the change from baseline to Week 52 significantly differed for the Basic and Augmented treatment strategies.

[b] Difference between groups at Week 52, determined by mixed model simple main effects test.

[c] Square root transformation.

[d] Impairment defined as often or very often. Basic (baseline [BL] and Week 52) $n = 20$; augmented (BL and Week 52) $n = 23$.

[e] Fisher's exact test, Week 52 data.

SUPPLEMENT 2

Outcome Analyses for Groups Defined According to Number of Medications at Week 52

Statistical analyses. Groups receiving None (n = 18), Single (n = 32), and Multiple (n = 58) medications were compared using analysis of variance (ANOVA) or Kruskal-Wallis depending on distribution of the data, for quantitative outcomes, or Fisher's exact test for categorical outcomes. For outcomes where significant omnibus tests were found, pairwise comparisons were explored with p values adjusted by the Bonferroni method. For the significant findings at Week 52, none of the baselines differed between groups. For Week 52 medication assessments, the group not receiving any medications (None) had higher mean item CASI-4R Schizophrenia Spectrum Disorder and Anger Irritability Symptom scores at baseline than single and multiple medication groups; however, when controlling for the baseline value, none of the group assignment effects changed.

Behavioral outcomes. No group differences were found for any of the behavioral outcome measures.

Safety outcomes. There was a significant main effect of weight (p = .0477), and there was a significant difference (p = .0138) between none vs. single regimens, with the former at higher weight (Table S4). For prolactin (quantitative value), there was a significant difference between single vs. multiple (p = .0003), with the multiple group having higher prolactin levels (Table S4). For the prolactin threshold (>18ng/mL for boys, >30ng/mL for girls), a higher proportion of those in the multiple group had elevated prolactin levels, compared to none or single.

Table S4: Week 52 Weight and Prolactin Comparisons Between None, Single, and Multiple Medication Regimens

Outcome Measure	None	Single	Multiple	*p* Value[a]
Weight	*n*=18	*n*=31	*n*=58	
Weight-for-age *z*-score, mean (SD)	0.94 (1.50)	0.09 (1.05)	0.44 (1.01)	.0477
Height				
Height-for-age *z*-score, mean (SD)	0.60 (1.41)	0.30 (0.98)	0.04 (0.85)	.1302
Prolactin	*n*=15	*n*=29	*n*=53	
Prolactin (ng/mL), mean (SD)	8.29 (4.49)	6.61 (4.54)	19.01 (14.73)	.0002
Prolactin elevated threshold (1)				
No	15 (100.0%)	28 (96.6%)	30 (56.6%)	<.0001
Yes	0 (0.0%)	1 (3.4%)	23 (43.4%)	
Prolactin elevated threshold (2)				
No	15 (100.0%)	29 (100.0%)	52 (98.1%)	1.0000
Yes	0 (0.0%)	0 (0.0%)	1 (1.9%)	

Note: Threshold definitions: (1) boys, > 18ng/mL; girls, > 30ng/mL and (2) Prolactin > 50ng/mL (boys or girls).

[a] Omnibus test for group comparisons

SUPPLEMENT 3

Outcome Analyses for Groups Defined According to Basic or Augmented Status at Week 52

Statistical analyses. Two strategies were used to parse particpants: one strategy was based on drug class consistent with original definition of Basic (stimulant, $n = 28$) and Augmented (stimulant, atypical neuroleptic; $n = 35$). This excluded all children receiving other concomitant medications. The second was based on the reason (indication) for which medication was prescribed and included concomitant medications as long as they were not prescribed for ADHD/aggression: Augmented Indications ($n = 40$) vs. Basic Indications ($n = 32$). For these analyses, groups were compared via two-sample *t*-test or Mann-Whitney U test, depending on distribution of the data, for quantitative outcomes or Fisher's exact test for categorical outcomes. For the significant findings at Week 52, none of the baselines differed between groups. For Week 52 Indications strategy, Augmented Indications had a higher mean item CASI-4R Schizophrenia Spectrum Disorder score at baseline than Basic Indications, however when controlling for the baseline value, none of the treatment effects changed.

Behavioral outcomes. The Augmented Indications group had higher scores on the Positive Social NCBRF scale (Table S5A). The Original Augmented group had lower scores on the ABS Instrumental (Proactive) Aggression scale. The Basic group (Original and Indications) had higher mean item scores on the Schizophrenia subscale of the CASI-4R. For the Indications strategy, CASI-4R Schizophrenia Spectrum Disorder mean item scores differed (with Augmented Indications having a higher score at baseline than Basic Indications), however when controlling for the baseline value, none of the treatment effects changed.

Table S5A: Analyses for Week 52 Differences Between Groups Defined in Terms of Original Drug Class (Original Basic, Original Augmented) and Indications (Basic Indications, Augmented Indications) at Week 52

	Original Drug Class[a]			Indications[b]		
	Basic	*Augmented*		*Basic*	*Augmented*	
Outcome Measure	n = 28	n = 35	*p* Value	n = 32	n = 40	*p* Value
NCBRF, mean (SD)						
D-Total	22.2 (16.1)	16.6 (12.1)	.1193	23.4 (16.0)	17.7 (12.1)	.0872
Positive social	15.5 (5.8)	19.5 (5.2)	.0054	15.4 (5.6)	18.4 (5.8)	.0328
Overly sensitive	4.0 (2.8)	3.1 (2.6)	.1832	3.9 (2.7)	3.1 (2.6)	.1843
ADHD	12.1 (7.6)	9.2 (6.1)	.1043	12.3 (7.2)	9.7 (6.0)	.0930
Withdrawn-dysphoric	8.6 (8.3)	4.9 (4.3)	.1319	8.8 (8.1)	5.3 (4.4)	.1166
ABS, mean (SD)						
Proactive	16.2 (4.7)	14.0 (3.8)	.0430	16.3 (4.7)	14.6 (4.0)	0.0918
Reactive	12.5 (3.4)	11.5 (2.4)	.1813	12.7 (3.2)	11.9 (2.6)	0.2240
CASI – mean item score, mean (SD)						
ADHD	1.20 (0.66)	0.97 (0.52)	.1706	1.25 (0.64)	1.01 (0.52)	0.1061
Attention	1.31 (0.73)	1.02 (0.52)	.1758	1.37 (0.74)	1.04 (0.52)	0.0913
Hyperactivity-impulsivity	1.10 (0.69)	0.91 (0.65)	.2412	1.14 (0.70)	0.97 (0.64)	0.3484
Hyperactivity	0.98 (0.77)	0.80 (0.70)	.3027	1.01 (0.79)	0.87 (0.70)	0.4757
Impulsivity	1.24 (0.72)	1.05 (0.72)	.2697	1.30 (0.73)	1.10 (0.70)	0.2825
ODD	1.28 (0.74)	1.01 (0.61)	.1612	1.36 (0.76)	1.08 (0.61)	0.1236
Anger irritability symp.	1.24 (0.86)	0.93 (0.64)	.1827	1.30 (0.85)	0.99 (0.64)	0.1317
Noncompliance	1.30 (0.73)	1.06 (0.64)	.1690	1.39 (0.76)	1.13 (0.65)	0.1331
Conduct disorder	0.23 (0.27)	0.14 (0.19)	.0910	0.24 (0.31)	0.16 (0.20)	0.1997
Peer conflict scale	0.77 (0.74)	0.49 (0.63)	.1074	0.74 (0.74)	0.57 (0.65)	0.3824
Physical aggression	0.82 (0.79)	0.51 (0.70)	.0690	0.78 (0.78)	0.62 (0.74)	0.3116
Nonphysical aggression	0.88 (0.87)	0.56 (0.68)	.1350	0.86 (0.87)	0.63 (0.70)	0.2486
Object aggression	0.45 (0.74)	0.30 (0.58)	.5037	0.44 (0.73)	0.38 (0.62)	0.9587
Generalized anxiety	0.55 (0.52)	0.48 (0.37)	.8340	0.55 (0.49)	0.52 (0.41)	0.9863
Other anxiety	0.24 (0.31)	0.15 (0.24)	.1068	0.26 (0.31)	0.19 (0.24)	0.2675
Social phobia	0.32 (0.55)	0.13 (0.26)	.2256	0.31 (0.54)	0.19 (0.31)	0.5694
Separation anxiety	0.18 (0.41)	0.16 (0.24)	.6743	0.18 (0.40)	0.19 (0.26)	0.4423
Schizoid personality disord.	0.37 (0.65)	0.30 (0.44)	.7288	0.42 (0.69)	0.35 (0.46)	0.6342

Enuresis, encopresis	0.23 (0.40)	0.11 (0.37)	.0599	0.23 (0.40)	0.14 (0.36)	0.1765
Schizophrenia	0.14 (0.23)	0.06 (0.16)	.0230	0.14 (0.21)	0.07 (0.16)	0.0191
Depression	0.23 (0.27)	0.11 (0.14)	.0765	0.22 (0.26)	0.12 (0.14)	0.1538
Manic symptoms	0.33 (0.39)	0.20 (0.27)	.1601	0.33 (0.37)	0.24 (0.32)	0.2212
Autism spectrum	0.35 (0.42)	0.19 (0.23)	.3564	0.35 (0.40)	0.22 (0.24)	0.3774
Anorexia	0.26 (0.37)	0.14 (0.25)	.1302	0.25 (0.35)	0.18 (0.33)	0.2464
Bulimia nervosa	0.13 (0.26)	0.16 (0.29)	.6865	0.12 (0.25)	0.14 (0.28)	0.5518
Anxiety composite	0.35 (0.37)	0.25 (0.22)	.3172	0.36 (0.36)	0.30 (0.25)	0.5021
Schizophrenia spectrum disorder	0.22 (0.29)	0.14 (0.22)	.3702	0.23 (0.30)	0.16 (0.22)	0.5253
CASI–Impairment, % impaired[c]						
ADHD	8 (28.6%)	11 (31.4%)	1.0000	11 (34.4%)	14 (35.0%)	1.0000
ODD	7 (25.9%)	9 (26.5%)	1.0000	10 (32.3%)	12 (30.8%)	1.0000
Conduct disorder	3 (10.7%)	0 (0.0%)	.0825	4 (12.5%)	0 (0.0%)	0.0350
Peer Conflict Scale	5 (21.7%)	0 (0.0%)	.0143	6 (22.2%)	1 (3.1%)	0.0402
Generalized anxiety	3 (10.7%)	2 (5.7%)	.6480	3 (9.4%)	2 (5.0%)	0.6498
Social phobia	1 (3.7%)	0 (0.0%)	.4355	1 (3.2%)	0 (0.0%)	0.4366
Separation anxiety	1 (3.6%)	0 (0.0%)	.4444	1 (3.1%)	0 (0.0%)	0.4444
Schizoid personality disord.	1 (3.6%)	1 (2.9%)	1.0000	2 (6.3%)	1 (2.5%)	0.5815
Schizophrenia	0 (0.0%)	1 (2.9%)	1.0000	0 (0.0%)	1 (2.5%)	1.0000
Depression	1 (3.6%)	3 (8.6%)	.6224	1 (3.1%)	3 (7.5%)	0.6239
Manic symptoms	1 (3.6%)	3 (8.6%)	.6224	1 (3.1%)	4 (10.0%)	0.3732
Autism spectrum	3 (10.7%)	0 (0.0%)	.0825	3 (9.4%)	1 (2.5%)	0.3166
Anorexia	2 (7.1%)	0 (0.0%)	.1935	2 (6.3%)	1 (2.5%)	0.5815
Bulimia nervosa	0 (0.0%)	0 (0.0%)	N/A	0 (0.0%)	0 (0.0%)	N/A
CGI-I, % much/very much improved	18 (64.3%)	28 (80.0%)	.2531	20 (62.5%)	33 (82.5%)	0.0655
CGI-S, % nonclinical	15 (53.6%)	25 (71.4%)	.1903	16 (50.0%)	27 (67.5%)	0.1533

Note: Comparisons at Week 52 for treatment groups were analyzed via two-sample *t*-test or Mann-Whitney *U* test, depending on distribution of the data, for quantitative outcomes or Fisher's exact test for categorical outcomes. ABS = Antisocial Behavior Scale; ADHD = attention-deficit/hyperactivity disorder; CASI = Child and Adolescent Symptom Inventory; CD = conduct disorder; CGI = Clinical Global Impressions; I = impairment; NCBRF = Nisonger Child Behavior Rating Form; ODD = oppositional defiant disorder; S = severity.

[a] Treatment group status at Week 52 defined in terms of the type of medication (i.e., drug class) that met our original criteria for Basic (stimulant) and Augmented (stimulant, atypical antipsychotic) but excludes children who were receiving any other types of concomitant psychotopric medication prescribed for problems other than ADHD or aggression.

[b] Treatment group status at Week 52 defined in terms of the type of medication (i.e., drug class) that met our original criteria for Basic (stimulant) and Augmented (stimulant, atypical antipsychotic) and includes children who were receiving concomitant psychotropic medication prescribed for problems (indications) other than ADHD or aggression.
[c] Impairment defined as often or very often.

A larger proportion of those in the Basic Indications group were impaired for conduct disorder (CASI-4R) than the Augmented Indications group. A larger proportion of those in the Basic group (Original and Indications) were impaired for the Peer Conflict Scale than those in the Augmented group. Of note is the finding that when CASI-4R Impairment cutoff is defined as sometimes, often, or very often, the conduct disorder impairment comparison was no longer significant (Basic Indications 38% impaired vs. 25% for Augmented Indications, $p = .31$). Similarly, the statistical significance for the Peer Conflict Scale was also diminished: Original Basic = 52% vs. 43% Original Augmented = 43%, $p = .78$, and Basic Indications = 52% vs. Augmented Indications = 50%, $p = 1.00$, respectively.

Safety outcomes. Group comparisons at Week 52 were analyzed via two-sample *t*-test or Mann-Whitney U test, depending on distribution of the data. Those in the Augmented group (Original and Indications) had higher weight-for-age *z*-scores (Table S5B).

Table S5B: Week 52 Vital Outcome Measure (Mean, Standard Deviation [SD]) Comparisons Between Basic Versus Augmented Groups

	Original Drug Class[a]			Indications[b]		
	Basic	*Augmented*		*Basic*	*Augmented*	
Outcome Measure	*n*=28	*n*=35	*p* Value	*n*=32	*n*=40	*p* Value
Weight-for-age *z*-score	0.16 (1.05)	0.57 (0.99)	.0648	0.05 (1.02)	0.53 (0.95)	.0199
Heart rate	83.5 (24.7)	86.7 (14.0)	.5502	82.8 (23.4)	85.9 (13.8)	.5117
Systolic blood pressure	102.5 (26.8)	108.3 (9.7)	.2799	102.8 (25.5)	107.6 (10.0)	.3186
Diastolic blood pressure	64.6 (19.1)	66.5 (8.7)	.6288	65.1 (18.0)	66.5 (8.5)	.6846
Height-for-age *z*-score	0.39 (0.96)	0.22 (0.79)	.5753	0.30 (0.93)	0.17 (0.82)	.6544

Note:
[a] Treatment group status at Week 52 defined in terms of the type of medication (i.e., drug class) that met our initial criteria for Basic (stimulant) and Augmented (stimulant, atypical antipsychotic) but excludes children who were receiving any other types of concomitant psychotopric medication prescribed for problems other than attention-deficit/hyperactivity disorder (ADHD) or aggression.
[b] Treatment group status at Week 52 defined in terms of the type of medication (i.e., drug class) that met our original criteria for Basic (stimulant) and Augmented (stimulant, atypical antipsychotic) and includes children who were receiving concomitant psychotropic medication prescribed for problems (indications) other than ADHD or aggression.

Prolactin. Comparisons at Week 52 for treatment groups (Original and Indications) were analyzed via Mann-Whitney U tests for quantitative outcomes or Fisher's exact test for categorical outcomes. Those in the Augmented group (Original and Indications) had higher prolactin levels (> 50ng/mL for boys or girls) (Table S5C). A higher proportion of those in the Augmented group (Original and Indications) were above the prolactin threshold (>18ng/mL for boys, >30ng/mL for girls) compared to the Basic group (52.9% Original Augmented vs. 3.7% Original Basic; 53.8% Augmented Indications 53.8% vs. 6.5% Basic Indications).

Extrapyramidal symptoms. Comparisons of AIMS and BARNES measures between treatment groups at Week 52 were not statistically significant. Most children obtained a score of zero for both outcomes.

Table S5C: Week 52 Prolactin Measure Comparisons Between Basic Versus Augmented

	Original Drug Class[a]			Indications[b]		
	Basic	*Augmented*		*Basic*	*Augmented*	
Outcome Measure	*n*=27	*n*=34	*p* Value	*n*=31	*n*=39	*p* Value
Prolactin (ng/mL), M (SD)	6.08 (4.19)	21.56 (12.77)	<.0001	6.88 (7.06)	22.35 (14.76)	<.0001
Prolactin elevated threshold (1), n (%)						
No	26 (96.3)	16 (47.1)	<.0001	29 (93.5)	18 (46.2)	<.0001
Yes	1 (3.7)	18 (52.9)		2 (6.5)	21 (53.8)	
Prolactin elevated threshold (2), n (%)						
No	27 (100.0)	34 (100.0)	n/a	31 (100.0)	38 (97.4)	1.0000
Yes	0 (0.0)	0 (0.0)		0 (0.0)	1 (2.6)	

Note: Threshold definitions: (1) boys, > 18ng/mL; girls, > 30ng/mL and (2) Prolactin > 50ng/mL (boys or girls).

[a] Treatment group status at Week 52 defined in terms of the type of medication (i.e., drug class) that met our original criteria for Basic (stimulant) and Augmented (stimulant, atypical antipsychotic) but excludes children who were receiving any other types of concomitant psychotopric medication prescribed for problems other than attention-deficit/hyperactivity disorder (ADHD) or aggression.

[b] Treatment group status at Week 52 defined in terms of the type of medication (i.e., drug class) that met our original criteria for Basic (stimulant) and Augmented (stimulant, atypical antipsychotic) and includes children who were receiving concomitant psychotropic medication prescribed for problems (indications) other than ADHD or aggression.