Supplemental Online Content

Harstad E, Shults J, Barbaresi W, et al. α_2-Adrenergic Agonists or Stimulants for Preschool-Age Children With Attention-Deficit/Hyperactivity Disorder. *JAMA.* Published online May 4, 2021. doi:10.1001/jama.2021.6118

This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Medication Class Prescribed for Initial ADHD Medication by Developmental-Behavioral Pediatrician

Physician #	Number (%) Children Initiated on Alpha-2 Adrenergic Agonists (N=175)	Number (%) Children Initiated on Stimulants (N=321)[a]
1	17 (55%)	14 (45%)
2	16 (38%)	26 (62%)
3	12 (80%)	3 (20%)
4	11 (69%)	5 (31%)
5	8 (89%)	1 (11%)
6	8 (67%)	4 (33%)
7	8 (73%)	3 (27%)
8	8 (73%)	3 (27%)
9	5 (63%)	3 (38%)
10	5 (100%)	0 (0%)
11	5 (45%)	6 (55%)
12	5 (28%)	13 (72%)
13	5 (45%)	6 (55%)
14	5 (63%)	3 (38%)
15	4 (18%)	18 (82%)
16	4 (36%)	7 (64%)
17	4 (36%)	7 (64%)
18	3 (30%)	7 (70%)
19	3 (50%)	3 (50%)
20	3 (38%)	5 (63%)
21	3 (27%)	8 (73%)
22	3 (38%)	5 (63%)
23	2 (29%)	5 (71%)
24	2 (14%)	12 (86%)
25	2 (22%)	7 (78%)
26	2 (50%)	2 (50%)
27	2 (40%)	3 (60%)
28	2 (100%)	0 (0%)
29	2 (25%)	6 (75%)
30	2 (10%)	19 (90%)
31	1 (8%)	12 (92%)
32	1 (10%)	9 (90%)
33	1 (17%)	5 (83%)
34	1 (50%)	1 (50%)
35	1 (50%)	1 (50%)
36	1 (100%)	0 (0%)
37	1 (25%)	3 (75%)
38	1 (25%)	3 (75%)
39	1 (13%)	7 (88%)
40	1 (20%)	4 (80%)
41	1 (17%)	5 (83%)
42	1 (8%)	11 (92%)
43	1 (100%)	0 (0%)
44	1 (33%)	2 (67%)

45	0 (0%)	5 (100%)
46	0 (0%)	7 (100%)
47	0 (0%)	7 (100%)
48	0 (0%)	2 (100%)
49	0 (0%)	3 (100%)
50	0 (0%)	1 (100%)
51	0 (0%)	1 (100%)
52	0 (0%)	1 (100%)
53	0 (0%)	6 (100%)
54	0 (0%)	3 (100%)
55	0 (0%)	1 (100%)
56	0 (0%)	2 (100%)
57	0 (0%)	11 (100%)
58	0 (0%)	2 (100%)
59	0 (0%)	2 (100%)

[a]Clinician # missing for one child initiated on stimulant medication, thus N=321.

eTable 2. Number and Percentage (with 95% Confidence Interval) of Children with Varying Levels of Improvement by Medication Excluding N=108 Children with Co-existing Autism Spectrum Disorder

Medication Class					**Difference between Alpha-2 Adrenergic Agonist and Stimulant**
Level of Improvement[a]	**Alpha-2 Adrenergic Agonist (N=118)**		**Stimulants[b] (N=270)**		
Very Much Improved	29 (25%; 15 - 34%)		107 (40%; 32 - 47%)		-15% (-27% to -3%)
Much Improved	49 (42%; 31 - 52%)		108 (40% 32 - 48%)		2% (-11% to 15%)
No Improvement	40 (34%; 24 - 44%)		55 (20%; 15 - 26%)		14% (2% to 25%)
Specific Medication					
	Guanfacine (N=107)	**Clonidine[c] (N=11)**	**Methylphenidate[b] (N=242)**	**Amphetamine (N=28)**	
Very Much Improved	25 (23%; 14-33%)	4 (36%; 8-65%)	96 (40%; 32-48%)	11 (39%; 20-58%)	
Much Improved	44 (41%; 30-52%)	5 (45%; 16-75%)	99 (41%; 33-49%)	9 (32%; 14-50%)	
No Improvement	38 (36%; 25-46%)	2 (18%; 5-41%)	47 (19%; 14-25%)	8 (29%; 11-46%)	

[a]Level of improvement was inferred by the data abstractor applying the clinical global improvement (CGI) scale portions that were able to be abstracted from medical records, with minimally improved being collapsed with no change and worse, and separate categories for much improved and very much improved.
[b]One child who was treated with stimulant medication (specifically methylphenidate) did not have clinician # available and thus is excluded from these results, since the 95% confidence intervals provided are adjusted for clustering by clinician.
[c]Given the small sample size, results should be interpreted with caution, as indicated by the wide confidence intervals.

eTable 3. Frequency and Percentage (with 95% Confidence Intervals) of Commonly Reported Adverse Effects for Medications Excluding N=108 Children with Co-existing Autism Spectrum Disorder

Adverse Effect[a]	Alpha-2 Adrenergic Agonist (N=118)	Stimulants (N=270)[b]
Daytime sleepiness	40 (34%; 25 - 42%)	7 (3%; 1 - 4%)
Moodiness/irritability	38 (32%; 22 - 43%)	132 (49%; 41 - 57%)
Disruptive behavior	36 (31%; 20 - 41%)	64 (24%; 17 - 31%)
Difficulty with sleep	16 (14%; 7 - 20%)	58 (21%; 17 - 26%)
Headaches	11 (9%; 3 - 16%)	14 (5%; 2 - 9%)
Appetite suppression	10 (8%; 2 - 15%)	109 (40%; 32 - 48%)
Stomachaches	6 (5%; 1 - 9%)	40 (15%; 11 - 19%)
Skin picking or other repetitive behaviors	5 (4%; 0 - 8%)	34 (13%; 8 - 17%)

[a]The data abstraction form listed many known adverse effects, and an “other” category, and the presence or absence of each was abstracted from text within the medical records.
[b]One child who was treated with stimulant medication (specifically methylphenidate) did not have clinician # available and thus is excluded from these results, since the 95% confidence intervals provided are adjusted for clustering by clinician.

eFigure 1. Data Collection for Treatment Episodes and Conversion to Treatment Intervals for Sample Participant

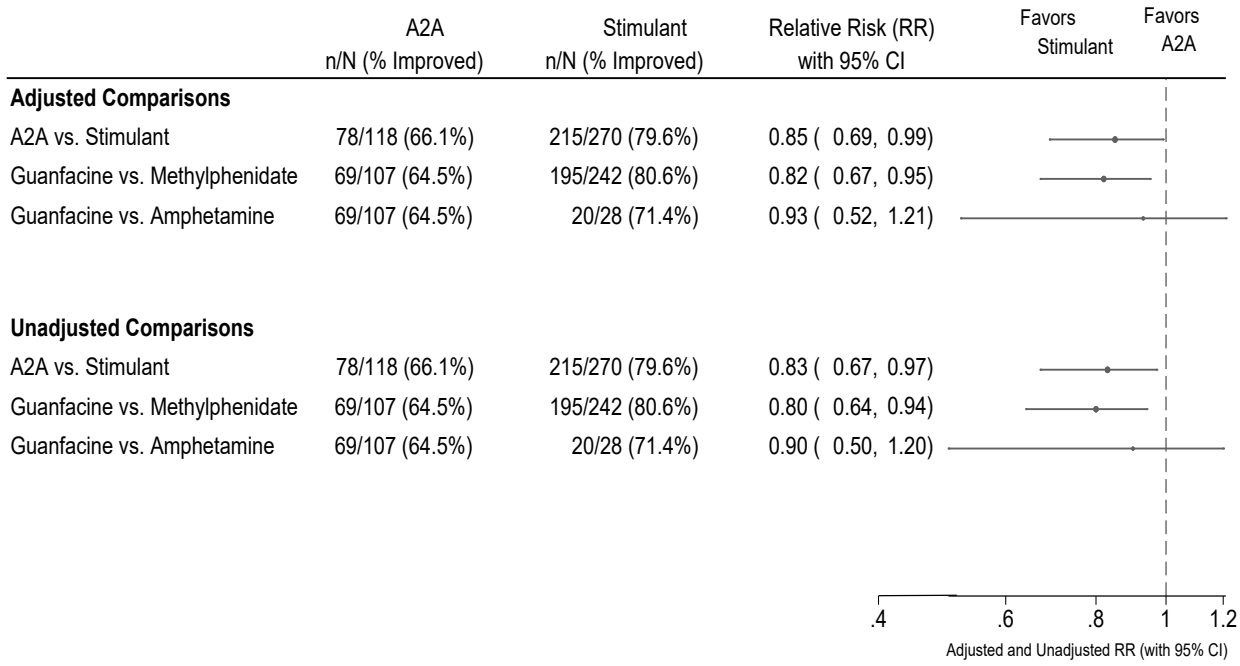
Treatment Episodes	Data Abstracted from the Medical Records at the Level of Treatment Episode			
	Dates[a]	**Medication Prescribed**	**Medication Response[b]**	**Adverse Effects[c]**
#1	October 1, 2015 – November 30, 2015	Methylphenidate short acting 5 mg in morning	No Improvement	None reported
#2	November 30, 2015 – January 6, 2016	Methylphenidate short acting 10 mg in morning	Much Improved	Delayed sleep onset
#3	January 6, 2016 – June 3, 2016	Methylphenidate long acting 18 mg in morning	Very Much Improved	Decreased appetite without weight loss Moodiness/irritability

Conversion of Treatment Episodes into Treatment Interval

Treatment Interval (based on the 3 treatment episodes above)	Data Included in the Analyses at the Level of Treatment Interval			
	Dates	**Medication Prescribed**	**Medication Response[d]**	**Adverse Effects[e]**
#1	October 1, 2015 – June 3, 2016	Methylphenidate First total daily dose at which effective = 10 mg	Associated with Improvement	Delayed sleep onset Decreased appetite without weight loss Moodiness/irritability

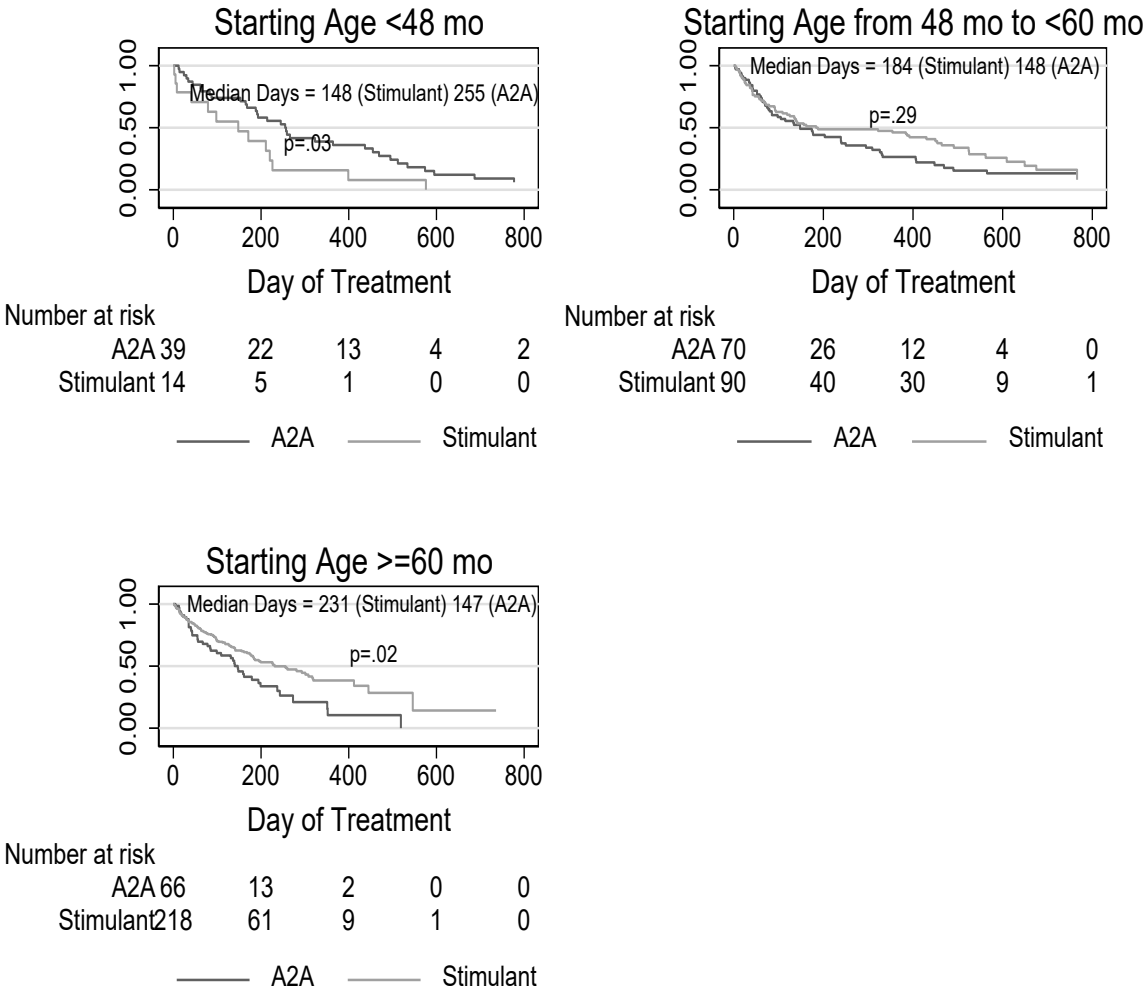
[a]Dates for treatment episode correspond with first date that a specific medication dose/frequency was used and last date that the specific medication dose/frequency was used. Dates for treatment interval encompass the start date of the first treatment episode and the end date of the last treatment episode.
[b]Each treatment episode had medication response coded as "Not effective"; "much improved"; or "very much improved" which was inferred from the narrative text within the medical records.
[c]All adverse effects that occurred within a treatment episode were abstracted.
[d]This treatment interval is coded as associated with improvement because at least one of the treatment episodes within the treatment interval was coded as associated with improvement.
[e]Any adverse effects included in any of treatment episodes are coded as present within the treatment interval.

eFigure 2. Forest Plot of Relative Risk for Improvement Excluding N=108 Children with Co-existing Autism Spectrum Disorder



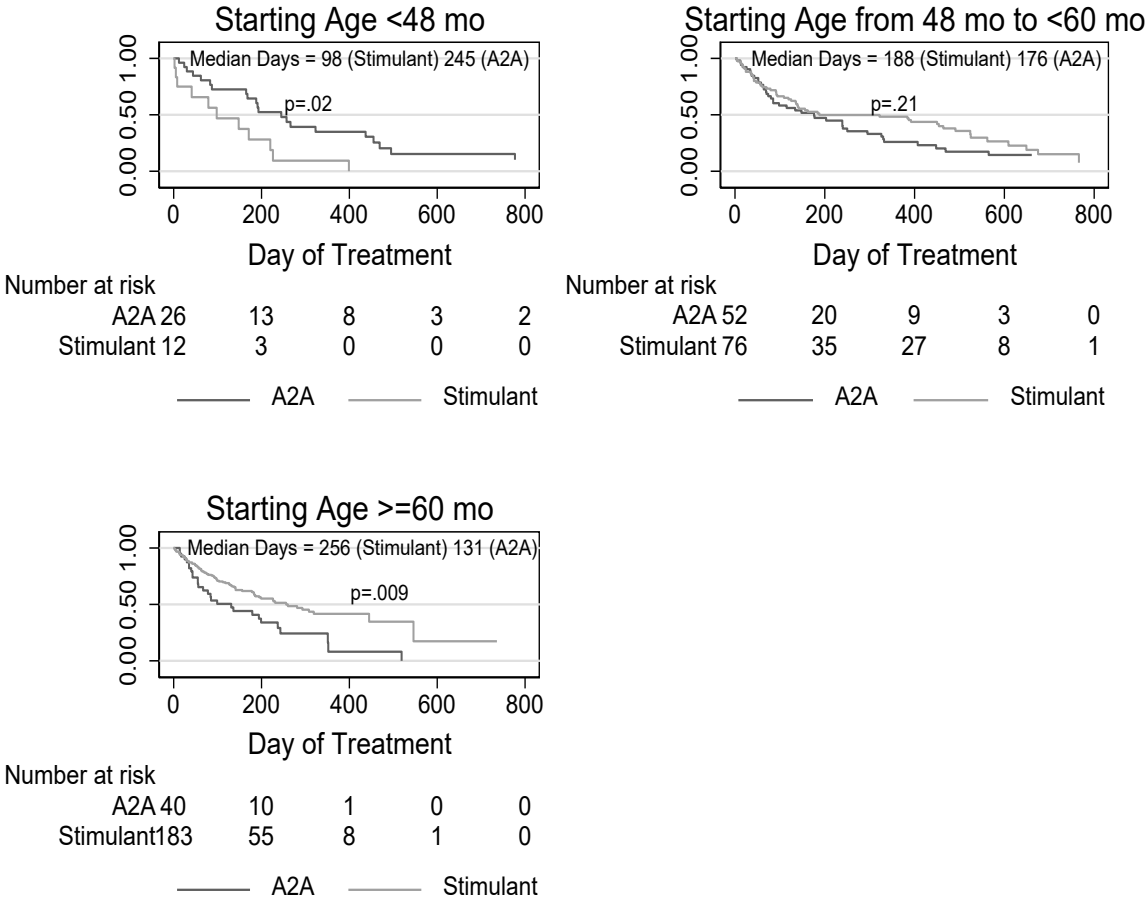
The estimated relative risks (RRs) and associated 95% CI were obtained by first fitting logistic regression models and then using the approach suggested in Zhang and Yu[23] to convert the estimated odds-ratios and their associated 95% CI to estimated RR (with 95% CI). The logistic models accounted for clustering within clinicians by site using the approach suggested by LaVange et al.[24] that applies survey methods, with clinician treated as the primary sampling unit and site as the stratification variable. The adjusted models included age, autism spectrum disorder, and sleep disorder.

eFigure 3. Length of Medication Treatment by Age



Prior to obtaining the graphs above, Cox models were fitted that included medication (stimulant versus A2A), age group, and age group by medication interaction terms. The Cox models accounted for clustering within clinicians by site using the approach suggested by LaVange et al.[24] that applies survey methods, with clinician treated as the primary sampling unit and site as the stratification variable. The proportional hazards (PH) assumption was evaluated by constructing log-log plots and plots of the observed survival curves versus the predicted Cox survival curves, using the stphplot and stcoxkm commands in Stata 16. The adjusted Wald test indicated that there was significant age by medication class interaction ($p = 0.006$), so separate Kaplan-Meier curves were constructed for each age group. The Peto-Peto-Prentice test was applied to compare the survival curves within age group. The Peto-Peto Prentice test is a nonparametric test that is robust to potential violations of the PH assumption. The median length of treatment interval for each medication class and age group (Median Days) was estimated as the minimum value of days of treatment at which the Kaplan-Meier product limit estimator of the survivor function is ≤ 0.50, i.e. it is the value at which the Kaplan-Meier survival curve crosses 0.50 in each of the above graphs.

eFigure 4. Length of Medication Treatment by Age Excluding N=108 Children with Co-existing Autism Spectrum Disorder



Prior to obtaining the graphs above, Cox models were fitted that included medication (stimulant versus A2A), age group, and age group by medication interaction terms. The Cox models accounted for clustering within clinicians by site using the approach suggested by LaVange et al.[24] that applies survey methods, with clinician treated as the primary sampling unit and site as the stratification variable. The proportional hazards (PH) assumption was evaluated by constructing log-log plots and plots of the observed survival curves versus the predicted Cox survival curves, using the stphplot and stcoxkm commands in Stata 16. The adjusted Wald test indicated that there was significant age by medication class interaction ($p<0.001$), so separate Kaplan-Meier curves were constructed for each age group. The Peto-Peto-Prentice test was applied to compare the survival curves within age group. The Peto-Peto Prentice test is a nonparametric test that is robust to potential violations of the PH assumption. The median length of treatment interval for each medication class and age group (Median Days) was estimated as the minimum value of days of treatment at which the Kaplan-Meier product limit estimator of the survivor function is ≤ 0.50, i.e. it is the value at which the Kaplan-Meier survival curve crosses 0.50 in each of the above graphs.