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α_2-Adrenergic Agonists or Stimulants for Preschool-Age Children With Attention-Deficit/Hyperactivity Disorder

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IMPORTANCE Attention-deficit/hyperactivity disorder (ADHD) is diagnosed in approximately 2.4% of preschool-age children. Stimulants are recommended as first-line medication treatment. However, up to 25% of preschool-age children with ADHD are treated with α_2-adrenergic agonist medications, despite minimal evidence about their efficacy or adverse effects in this age range.

OBJECTIVE To determine the frequency of reported improvement in ADHD symptoms and adverse effects associated with α_2-adrenergic agonists and stimulant medication for initial ADHD medication treatment in preschool-age children.

DESIGN, SETTING, AND PARTICIPANTS Retrospective electronic health record review. Data were obtained from health records of children seen at 7 outpatient developmental-behavioral pediatric practices in the Developmental Behavioral Pediatrics Research Network in the US. Data were abstracted for 497 consecutive children who were younger than 72 months when treatment with an α_2-adrenergic agonist or stimulant medication was initiated by a developmental-behavioral pediatrician for ADHD and were treated between January 1, 2013, and July 1, 2017. Follow-up was complete on February 27, 2019.

EXPOSURES α_2-Adrenergic agonist vs stimulant medication as initial ADHD medication treatment.

MAIN OUTCOMES AND MEASURES Reported improvement in ADHD symptoms and adverse effects.

RESULTS Data were abstracted from electronic health records of 497 preschool-age children with ADHD receiving α_2-adrenergic agonists or stimulants. Median child age was 62 months at ADHD medication initiation, and 409 children (82%) were males. For initial ADHD medication treatment, α_2-adrenergic agonists were prescribed to 175 children (35%; median length of α_2-adrenergic agonist use, 136 days) and stimulants were prescribed to 322 children (65%; median length of stimulant use, 133 days). Improvement was reported in 66% (95% CI, 57.5%-73.9%) of children who initiated α_2-adrenergic agonists and 78% (95% CI, 72.4%-83.4%) of children who initiated stimulants. Only daytime sleepiness was more common for those receiving α_2-adrenergic agonists vs stimulants (38% vs 3%); several adverse effects were reported more commonly for those receiving stimulants vs α_2-adrenergic agonists, including moodiness/irritability (50% vs 29%), appetite suppression (38% vs 7%), and difficulty sleeping (21% vs 11%).

CONCLUSIONS AND RELEVANCE In this retrospective review of health records of preschool-age children with ADHD treated in developmental-behavioral pediatric practices, improvement was noted in the majority of children who received α_2-adrenergic agonists or stimulants, with differing adverse effect profiles between medication classes. Further research, including from randomized clinical trials, is needed to assess comparative effectiveness of α_2-adrenergic agonists vs stimulants.

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Supplemental content

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The percentage of preschool-age children in the US diagnosed with attention-deficit/hyperactivity disorder (ADHD) was estimated to be 2.4% in 2016, and has been increasing over the past decade.[1] Preschool-age children with ADHD are at risk for expulsion from preschool[2] and future academic underachievement.[3] Behavioral treatment is recommended as initial ADHD intervention for young children, with consideration of methylphenidate treatment when behavioral treatment is insufficient.[4,5]

The Preschool ADHD Treatment Study, a randomized, placebo-controlled study of children aged 3 to 5.5 years with ADHD, found that methylphenidate significantly reduced ADHD symptoms.[6] However, during the open-label extension, more than 40% of children had irritability while receiving the medication and more than 20% had crying or were tearful/sad/depressed.[7]

Treatment with α_2-adrenergic agonists is common and increasing, despite very limited data in this age group.[8] A Kentucky Medicaid claims study of preschool-age children with ADHD found that α_2-adrenergic agonist monotherapy increased from 10% to 23% between 2012 and 2017, with higher rates of α_2-adrenergic agonist use for the youngest ages.[9] Although there are randomized clinical trials that have examined the use of α_2-adrenergic agonists in older children and adolescents,[10-12] published data on use of these medications in preschool-age children are limited to a 4-child case series[13] and scant information about a small number children aged 4 and 5 years included in studies focused on older children.[14,15]

Given the increasing use of α_2-adrenergic agonists for preschool-age children with ADHD, paucity of data on efficacy or adverse effects of α_2-adrenergic agonists, and recommendations for use of methylphenidate when medication is chosen, this retrospective medical records study of α_2-adrenergic agonists and stimulants for the treatment of preschool ADHD was conducted to determine reported improvement in ADHD symptoms associated with α_2-adrenergic agonist and stimulant medication for initial ADHD medication treatment in preschool-age children and evaluate the frequency of reported adverse effects of α_2-adrenergic agonists and stimulants.

Key Points

Question For preschool-age children with attention-deficit/hyperactivity disorder initiating α_2-adrenergic agonist or stimulant medications in developmental-behavioral pediatric practices, what improvements and adverse effects were noted?

Findings In this retrospective review of health records of 497 children, improvement was noted in 115 of 175 children (66%) who received α_2-adrenergic agonists and 251 of 322 children (78%) who received stimulants, with differences in adverse effect profiles noted between medication classes.

Meaning Further research from randomized clinical trials is needed to assess comparative effectiveness of α_2-adrenergic agonists vs stimulants for preschool-age children with ADHD.

Methods

Study Design and Participants

The Children's Hospital of Philadelphia Institutional Review Board determined that this study was exempt with waiver of consent, and other sites utilized reliance agreements. This was a retrospective medical record review study conducted by the Developmental Behavioral Pediatrics Research Network[16] investigators across 7 academic developmental-behavioral pediatric programs from diverse US geographical locations. Children were referred to these programs for developmental-behavioral concerns and evaluated for ADHD through assessment by developmental-behavioral pediatricians and, at some sites, child psychologists through multidisciplinary assessments. Inclusion criteria were ADHD diagnosis by a developmental-behavioral pediatrician (*ICD-10* codes F90.0-F90.9); prescription for an α_2-adrenergic agonist or stimulant by a developmental-behavioral pediatrician when the child was younger than 72 months; and receiving treatment between January 1, 2013, and July 1, 2017 (final date of medication follow-up was February 27, 2019). If a child treated during this timeframe initiated treatment before January 1, 2013, the visits before January 1, 2013, were also included in the data abstraction. Exclusion criteria were moderate or severe global developmental delay or intellectual disability diagnosis and/or documentation of an overall developmental or intelligence quotient less than 55; psychotropic medication use (stimulant, α_2-adrenergic agonist, selective serotonin reuptake inhibitor, antipsychotic, or mood stabilizer) at the time of, or prior to, the initial developmental-behavioral pediatric visit; or being prescribed an α_2-adrenergic agonist only for sleep (**Figure 1**).

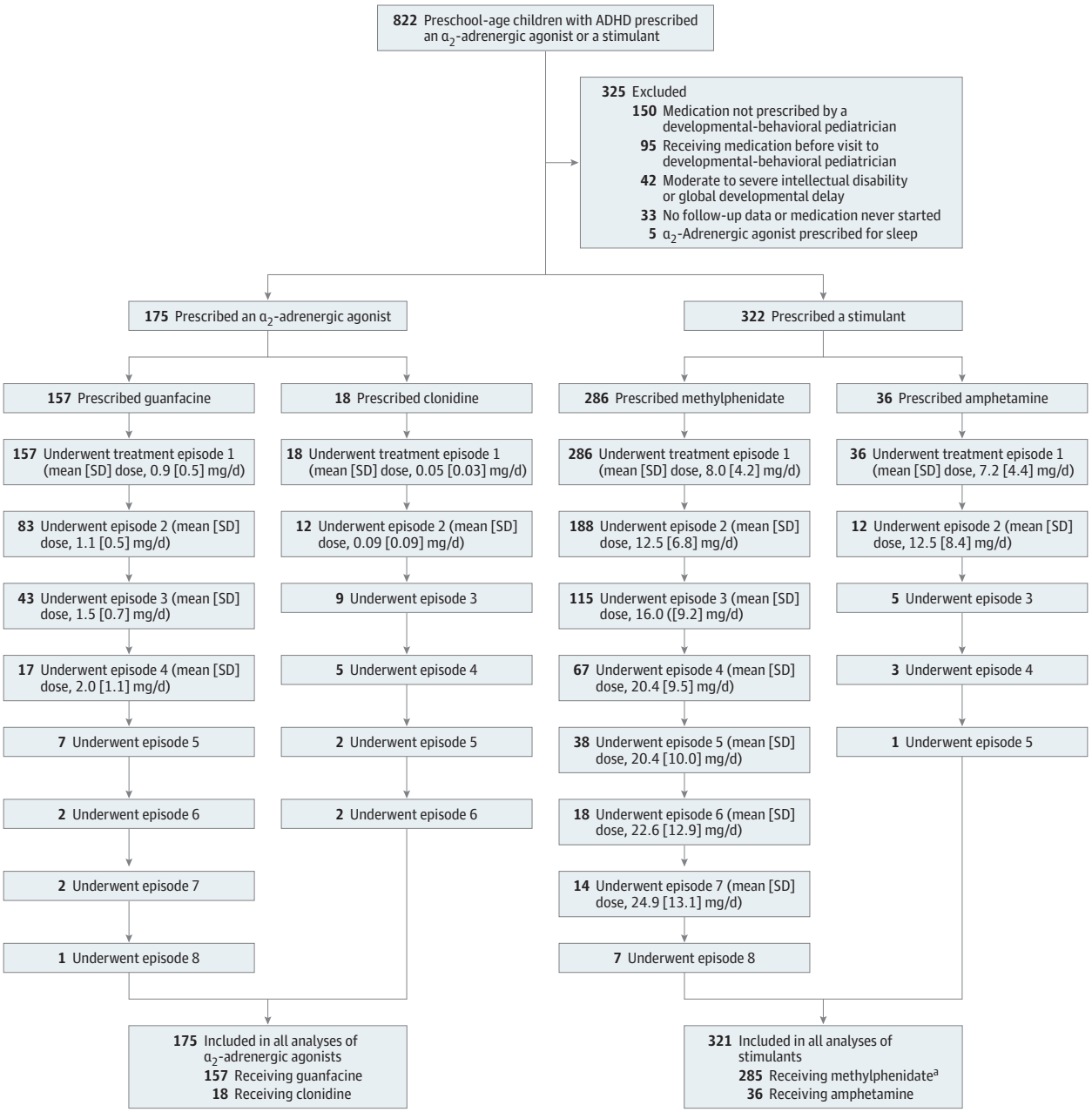
Data Abstraction Procedures

Development of Data Abstraction Protocol

The data abstraction form and guide were created through an iterative process modeled after previous studies.[17,18] All data abstractors completed data entry on 5 de-identified cases after training by the first author (E.H.). Data abstractors achieved proficiency with data collection (>85% consistency with criterion standard training case answers) prior to initiating chart reviews. Across the study, 16% of charts were double-coded, and interrater reliability had a mean of 98% for all variables.

Data abstracted from narrative records at every site included demographic information, coexisting conditions documented at the time of ADHD diagnosis, type and dose of medication used for ADHD, start and stop dates for medication treatment, reported improvement in ADHD symptoms, and adverse effects. Race and ethnicity were abstracted to determine possible association with first ADHD medication prescribed. Race/ethnicity were based on fixed categories entered into the medical records by administrative staff or clinicians. Data abstraction ended at the first visit after the child was older than 72 months or if a selective serotonin reuptake inhibitor or atypical antipsychotic was prescribed or no further information about medication was available in the record. We abstracted data about whether the child received counseling or therapy prior to initiating ADHD medication (responses dichotomized to yes or no).

Figure 1. Children Included in a Study of α_2-Adrenergic Agonists vs Stimulants for Preschool-Age Children With Attention-Deficit/Hyperactivity Disorder (ADHD)



Analyses were completed on first treatment interval, which consisted of all treatment episodes (defined as period of time during which child was prescribed a specific medication at a specific dose and specific frequency) for each medication. Mean dose is not reported for treatment episodes with less than 10 children.

[a] One child was excluded from an analysis that included adjusting for clustering by clinician because clinician data were missing.

Definition of Treatment Episodes and Intervals

We abstracted data about reported improvement and adverse effects for each treatment episode, defined as a period during which the child was prescribed a specific medication at a specific dose and a specific frequency. However, analyses were based on the first treatment interval, defined as the period during which a child was prescribed a specific medication class (guanfacine, clonidine, methylphenidate, amphetamine), regardless of dose, frequency, or formulation. We chose to conduct analyses of the first treatment interval to derive clinically meaningful results from our findings, consistent with approaches used in clinical trials, and to avoid missing improvement for medications with upward dose titration (eFigure 1 in the Supplement).

Outcomes

Primary Outcome: Medication Treatment Response

Data abstractors coded medication treatment response for each treatment episode using the clinical global improvement scale as a guide.[19] The clinical global improvement scale is a clinician-rated evaluation of improvement used in pharmacologic studies, ranging from 1 to 7, with a score of 1 indicating very much improved; 2, much improved; 3, minimally improved; and 4 to 7, no change or worsening. The data abstractor inferred the clinical global improvement scale score from the clinic notes, using precise instructions in the data abstraction guide about how to code specific phrases. For this study, a treatment was rated as "associated with improvement" during a treatment episode if the child was considered "very much improved" or "much improved" and as "no improvement" if the child's ADHD symptoms were minimally improved or worse or if the abstractor determined there to be insufficient data to judge improvement. The treatment interval was coded as "very much improved" if any single treatment episode in the first interval was rated as "very much improved." The treatment interval was coded as "much improved" if any single treatment episode was rated as "much improved" and none were rated as "very much improved." The treatment interval was coded as "no improvement" if none of the episodes were rated as "very much improved" or "much improved."

Primary Outcome: Adverse Effects

We abstracted data about any adverse effect that occurred during each treatment episode. The data abstraction form listed many known adverse effects and an "other" category, and the presence or absence of each adverse effect was abstracted from the medical records. For this study, we evaluated adverse effects throughout the first treatment interval.

Secondary Outcome: Medication Dosages

Dosages were recorded as total daily dose in milligrams. For dexmethylphenidate, the total daily dose was multiplied by 2 to generate an equivalent to methylphenidate dosing.

Analyses

The κ statistic was used to evaluate interobserver agreement on the ratings of no improvement vs improvement and on ratings of no improvement vs much improved vs very much improved for each treatment episode. Mean (SD) doses for dose of medication used in treatment intervals associated with improvement were compared with mean maximum doses of medication used in treatment intervals that were not associated with improvement using *t* tests (separately for guanfacine and methylphenidate).

Percentages and differences in the percentage of intervals rated as improved between medication groups (eg, α_2-adrenergic agonists or stimulants) were provided, with 95% CIs obtained using the prtest command in Stata, version 16.0 (StataCorp). The 95% CIs were adjusted for intraphysician correlation of measurements by specifying the correlation in the prtest command as the estimated correlation from a fitted exchangeable correlation structure in a logistic generalized estimating equation analysis of improvement associated with medication use. Adjusting for intraphysician correlation resulted in a slight widening of the 95% CIs. Logistic regression was then applied to account for potential confounders (age, autism spectrum disorder, sleep disorder) that were associated with prescription decisions for preschool-age children with ADHD in prior studies,[17,20] following Kraemer[21] and Bursac et al.[22] These variables were also significantly associated with the medication initiated (**Table 1**). Unadjusted analyses were also performed and the sensitivity of the results to the inclusion of other covariates was evaluated. The approach suggested by Zhang and Yu[23] was then used to correct the odds ratio and associated limits for the 95% CI so that they present an estimate of the relative risk.

Survival analysis techniques were applied to evaluate the duration of medication initially prescribed across age groups. Cox proportional hazards models were fitted, which included medication (α_2-adrenergic agonist vs stimulant), age group, and age group × medication interaction terms. The proportional hazards assumption was evaluated by constructing log-log plots and plots of the observed survival curves vs the predicted Cox survival curves, using the stphplot and stcoxkm commands in Stata, version 16. The adjusted Wald test indicated that there was a significant age × medication class interaction ($P = .006$), 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 groups. The Peto-Peto-Prentice test is a nonparametric test that is robust to potential violations of the proportional hazards assumption. The median length of treatment interval for each medication class and age group was estimated as the minimum number of days of treatment on which the Kaplan-Meier product limit estimator of the survivor function was less than or equal to 0.50 (ie, the day of treatment on which the Kaplan-Meier survival curve crosses 0.50 in each graph).

To address clustering within clinicians by site, the logistic and Cox models were implemented 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, to account for the nested data structure (patients nested within clinicians nested within sites).

The linearity in the logit assumption for age was evaluated graphically using the lincheck command in Stata, version 16. The hypothesis of goodness of fit for the logistic models were evaluated using an F-adjusted mean residual test for survey data.[25] Sensitivity analyses were performed that replicated regression logistic analysis for relative risk of treatment improvement only for the most commonly used α_2-adrenergic agonist (guanfacine) vs the most commonly used stimulant (methylphenidate). Additionally, sensitivity analyses replicated all analyses excluding the 108 children with autism spectrum disorder.

The RedCap surveys used required a response for each question. However, there was 1 missing value for medication dose and clinician identification. These 2 values were not imputed. The multivariable analyses that adjust for clustering by site and physician therefore include 1 fewer child than the unadjusted analyses; this is indicated when the results are presented.

Table 1. Participant Characteristics in a Study of α_2-Adrenergic Agonists vs Stimulants for Preschool-Age Children With Attention-Deficit/Hyperactivity Disorder (ADHD)

Characteristic	No. (%)	
	α_2-Agonist (n = 175)	Stimulant (n = 322)
Age at ADHD diagnosis, median (IQR), mo	54 (47-61)	60 (54-66)
Age at ADHD medication initiation, median (IQR), mo	56 (49-63)	63 (58-68)
Sex		
Male	147 (84)	262 (81)
Female	28 (16)	60 (19)
Insurance type		
Medicaid	98 (56)	178 (55)
Private	74 (42)	136 (42)
Tricare/self-pay/unknown	3 (2)	8 (2)
Race[a]	n = 167	n = 296
White	110 (66)	189 (64)
Black	34 (20)	60 (20)
Other	15 (9)	31 (10)
Asian	3 (2)	9 (3)
Mixed	4 (2)	3 (1)
American Indian	1	3 (1)
Pacific Islander	0	1
Ethnicity[a]	n = 165	n = 293
Non-Hispanic	145 (88)	247 (84)
Hispanic	20 (12)	46 (16)
Site		
1	15 (9)	93 (29)
2	37 (21)	21 (7)
3	8 (5)	19 (6)
4	70 (40)	80 (25)
5	37 (21)	34 (11)
6	5 (3)	34 (11)
7	3 (2)	41 (13)
Presence of coexisting conditions[b]		
Sleep disorder	64 (37)	75 (23)
Autism spectrum disorder	57 (33)	51 (16)
Disruptive behavior disorder	48 (27)	65 (20)
Mild global developmental delay[c]	22 (13)	38 (12)
Anxiety disorder	8 (5)	16 (5)
Behavioral therapy received prior to medication initiation[d]	89 (50.8)	136 (42.2)
Medication formulations prescribed[e]		
Methylphenidates		
Short-acting	198	
Metadate, controlled delivery	42	
Focalin, extended release	22	
Ritalin, long-acting	18	
Concerta	4	
Quillivant	1	
Daytrana	1	
Amphetamines		
Short-acting	23	
Adderall, extended release	7	
Dexedrine spansule	4	
Vyvanse	2	
Guanfacine		
Short-acting		155
GuanfacineER/Intuniv		2
Clonidine		
Short-acting		18

Abbreviation: IQR, interquartile range.

[a] Race and ethnicity were collected via record review and entered into the medical records by administrative staff and/or clinicians. "Other" was a categorical choice in the medical records. The percentages for race and ethnicity were based off of known data.

[b] Coexisting conditions were abstracted from the "formulation/impression" section of the medical record note in which the child was given a diagnosis of ADHD by a developmental-behavioral pediatrician.

[c] Exclusion criteria included moderate and severe global developmental delay, thus only mild global developmental delay is reported as a coexisting condition. Mild global developmental delay indicates mild delays in meeting developmental milestones.

[d] Behavioral therapy included parent management therapy, applied behavioral analysis, or other mention of counseling or therapy for ADHD.

[e] The data abstraction form did not specify what formulation among short-acting options and included the following groups: short-acting methylphenidate (Ritalin, Focalin, Methylin); short-acting amphetamine (Adderall, Dexedrine, ProCentra, Zenzedi, Evekeo); short-acting guanfacine (guanfacine, Tenex); and short-acting clonidine (Clonidine, Catapres).

Analyses were conducted using Stata, version 16.0, with 2-sided tests of hypotheses and *P* value <.05 as the criterion for statistical significance. Because of the potential for type I error due to multiple comparisons, findings for secondary end points and analyses should be interpreted as exploratory.

Results

Participants/Demographics

Data were abstracted from electronic health records of 497 preschool-age children with ADHD being treated with α_2-adrenergic agonists or stimulants across 7 sites. The median (interquartile range) age of children at initial ADHD medication use was 62 (54-67) months. Overall, 409 (82%) children were male. Of 463 children with race data available, 299 (65%) were White, and of 458 children with ethnicity data available, 392 (86%) were non-Hispanic. Across all groups, records indicated that 225 children (45%) received behavior therapy prior to the initiation of medication (Table 1). The first medication prescribed to manage ADHD was an α_2-adrenergic agonist for 175 children (35%), with 157 prescribed guanfacine preparations and 18 prescribed

Table 2. Improvement by Medication Type in a Study of α_2-Adrenergic Agonists vs Stimulants for Preschool-Age Children With Attention-Deficit/Hyperactivity Disorder

	No. (%) [95% CI]		
Level of improvement[a]	α_2-Adrenergic agonist (n = 175)	Stimulants (n = 321)[b]	Difference (95% CI)
Very much improved	43 (25) [16 to 33]	121 (38) [30 to 46]	−13 (−25 to −1)
Much improved	72 (41) [32 to 50]	129 (40) [33 to 47]	1 (−10 to 12)
No improvement	60 (34) [26 to 42]	71 (22) [17 to 28]	12 (2 to 22)

[a] Level of improvement was inferred by the data abstractor applying the clinical global improvement 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 the clinician identification number available and thus was excluded from these results because the 95% CIs provided were adjusted for clustering by clinician.

Table 3. Improvement by Specific Medication in a Study of α_2-Adrenergic Agonists vs Stimulants for Preschool-Age Children With Attention-Deficit/Hyperactivity Disorder

	No. (%) [95% CI]			
Level of improvement[a]	Guanfacine (n = 157)	Clonidine (n = 18)[b]	Methylphenidate (n = 285)[c]	Amphetamine (n = 36)
Very much improved	36 (23) [14 to 32]	7 (39) [15 to 63]	108 (38) [30 to 46]	13 (36) [19 to 53]
Much improved	64 (41) [31 to 50]	8 (44) [20 to 68]	119 (42) [34 to 49]	10 (28) [12 to 43]
No improvement	57 (36) [28 to 45]	3 (17) [0 to 34]	58 (20) [15 to 26]	13 (36) [20 to 52]

[a] Level of improvement was inferred by the data abstractor applying the clinical global improvement 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] Given the small sample size, results should be interpreted with caution, as indicated by the wide CIs.

[c] One child who was treated with stimulant medication (specifically methylphenidate) did not have the clinician identification number available and thus was excluded from these results because the 95% CIs provided were adjusted for clustering by clinician.

clonidine preparations. Stimulants were prescribed for 322 (65%) children, with 286 prescribed methylphenidate-based preparations and 36 prescribed amphetamine-based preparations. For α_2-adrenergic agonists, 99% of children were prescribed the immediate-release medications; for stimulants, 69% of children were prescribed short-acting formulations. Of the 59 different developmental-behavioral pediatricians who prescribed ADHD medication to preschool-age children during the study period, 4 prescribed only α_2-adrenergic agonists, 15 prescribed only stimulants, and 40 prescribed both (eTable 1 in the Supplement).

Reported Improvement in ADHD Symptoms Associated With Medication Treatment

α_2-Adrenergic agonists prescribed for the first treatment interval were rated as "associated with improvement" for 115 of 175 intervals (66% [95% CI, 57.5%-73.9%]), and stimulants were rated as "associated with improvement" for 251 of 322 intervals (78% [95% CI, 72.4%-83.4%]) (difference, 12% [95% CI, 2.3%-22.0%]). Children receiving α_2-adrenergic agonists were less likely to be rated as "very much improved" compared with those receiving stimulants (25% [95% CI, 17.2%-32.0%] vs 38% [95% CI, 31.3%-44.1%]; difference, 13% [95% CI, 1.4%-24.9%]) (**Table 2**; **Table 3**).

The κ statistic was 0.96 for interobserver agreement of improved vs not improved and was 0.75 for the rating of not improved vs much improved vs very much improved.

The logistic regression analysis demonstrated that the relative risk of treatment being associated with improvement was significantly lower for α_2-adrenergic agonists vs stimulants (relative risk, 0.87 [95% CI, 0.72-1.00]; goodness-of-fit *P* value = .33). Repeating this analysis including only the most commonly used α_2-adrenergic agonist (guanfacine) vs the most commonly used stimulant (methylphenidate) yielded similar results (**Figure 2**).

For guanfacine, the mean (SD) dose used when improvement was first reported was less than the mean (SD) maximum dose used when the medication was not associated with improvement (0.90 [0.5] vs 1.10 [0.6] mg/d; *P* = .04). For methylphenidate, there was no significant difference in the mean (SD) dose used when improvement was first reported and the mean (SD) maximum dose used when the medication was not associated with improvement (9.60 [5.4] vs 9.60 [6.2] mg/d; *P* = .94).

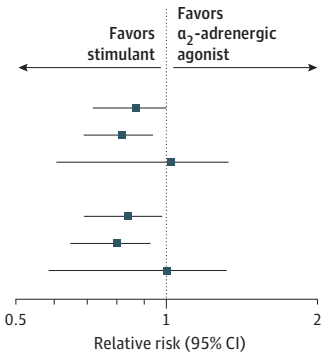
Adverse Effects

The most commonly reported adverse effects for α_2-adrenergic agonists were daytime sleepiness (38%) and increased moodiness/irritability (29%). For stimulants, the most commonly reported adverse effects were increased moodiness/irritability (50%) and appetite suppression (38%). The only adverse effect reported more often for children receiving α_2-adrenergic agonists than for children receiving stimulants was increase in daytime sleepiness (38% vs 3%; **Table 4**); several adverse effects were reported more often in children receiving stimulants, including appetite suppression (38% vs 7%), increased moodiness/irritability (50% vs 29%), difficulty falling asleep (21% vs 11%), increased stomachaches (13% vs 5%), and increased skin picking/repetitive behaviors (11% vs 5%).

Sensitivity analyses in which the 108 children with autism spectrum disorder were excluded yielded similar results for reported medication improvement, relative risk,

Figure 2. Outcomes in a Study of α2-Adrenergic Agonists vs Stimulants for Preschool-Age Children With Attention-Deficit/Hyperactivity Disorder

	No. improved/total No. (%)		
	α2-Adrenergic agonist	Stimulant	Relative risk (95% CI)
Adjusted comparisons			
α2-Adrenergic agonist vs stimulant	115/175 (65.7)	250/321 (77.9)	0.87 (0.72-1.00)
Guanfacine vs methylphenidate	100/157 (63.7)	227/285 (79.6)	0.82 (0.69-0.94)
Guanfacine vs amphetamine	100/157 (63.7)	23/36 (63.9)	1.02 (0.61-1.32)
Unadjusted comparisons			
α2-Adrenergic agonist vs stimulant	115/175 (65.7)	250/321 (77.9)	0.84 (0.69-0.98)
Guanfacine vs methylphenidate	100/157 (63.7)	227/285 (79.6)	0.80 (0.65-0.93)
Guanfacine vs amphetamine	100/157 (63.7)	23/36 (63.9)	1.00 (0.59-1.31)



The estimated relative risks and associated 95% CIs for reported medication improvement 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% CIs to estimated relative risks. 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.

and adverse effects (eTable 2, eFigure 2, and eTable 3 in the Supplement).

Duration of Treatment

The median (interquartile range) length of first treatment interval was 136 (49-258) days for the α2-adrenergic agonist group and 133 (48-252) days for the stimulant group. However, there was significant age at initiation of treatment × medication class (α2-adrenergic agonist vs stimulant) interaction (P = .006). Thus, separate Kaplan-Meier curves were developed for children with treatment initiated at younger than 4 years, 4 to younger than 5 years, and 5 to younger than 6 years. Children younger than 4 years initially prescribed α2-adrenergic agonists were likely to continue receiving these medications longer than those prescribed stimulants (eFigure 3 and eFigure 4 in the Supplement). In contrast, children who were aged 5 to younger than 6 years when they started receiving medication were likely to continue receiving the medication longer if they were prescribed a stimulant. There were no significant differences between the Kaplan-Meier curves for the children prescribed medication when they were aged 4 to younger than 5 years.

Discussion

In this retrospective review of health records of preschool-age children with ADHD treated across developmental-behavioral pediatric sites, improvement was noted in the majority of children who initiated α2-adrenergic agonists or stimulants, with differing adverse effect profiles between medication classes. To our knowledge, this is the first study to report on medication response and adverse effects for preschool-age children treated with α2-adrenergic agonist and stimulant medications for ADHD.

Of children prescribed medication, many had no mention of receipt of previous or concurrent behavioral therapy in the health record at the time of ADHD medication initiation.

Table 4. Adverse Effects in a Study of α2-Adrenergic Agonists vs Stimulants for Preschool-Age Children With Attention-Deficit/Hyperactivity Disorder

	No. (%) [95% CI]	
Adverse effect[a]	α2-Adrenergic agonist (n = 175)	Stimulants (n = 321)[b]
Daytime sleepiness	66 (38) [30-45]	9 (3) [1-5]
Moodiness/irritability	50 (29) [21-36]	161 (50) [43-57]
Disruptive behavior	49 (28) [19-37]	72 (22) [16-29]
Difficulty with sleep	19 (11) [6-15]	67 (21) [17-25]
Headaches	16 (9) [5-13]	16 (5) [3-7]
Appetite suppression	13 (7) [3-12]	123 (38) [33-44]
Stomachaches	8 (5) [1-8]	42 (13) [9-17]
Skin picking or other repetitive behaviors	8 (5) [1-8]	36 (11) [7-15]

[a] The data abstraction form listed many known adverse effects and an "other" category, and the presence or absence of each was abstracted from the medical records.

[b] One child who was treated with stimulant medication (methylphenidate) did not have the clinician identification number available and thus was excluded from these results because the 95% CIs provided were adjusted for clustering by clinician.

These findings are consistent with other reports.[1,26] The finding that α2-adrenergic agonists alone were prescribed to 35% of preschool-age children with ADHD is also consistent with previously reported ranges of 23% to 33%.[9,17,20] The initial medication prescribed for ADHD was evaluated in previously medication-naive preschool children in this study, which suggests that developmental-behavioral pediatricians frequently initiate α2-adrenergic agonist treatment in this age group despite clinical practice guidelines recommending methylphenidate treatment.[4,5]

Clinicians may prefer to initiate treatment with α2-adrenergic agonists vs stimulants due to concern about adverse effects. The Preschool ADHD Treatment Study (PATS) reported high rates of adverse effects when preschool children were treated with stimulants.[7] In the current study, compared with PATS, there were similar rates of

moodiness/irritability (50% vs 44%), trouble sleeping (21% vs 29%), and stomachaches (13% vs 17%). In the current study, those adverse effects occurred more often with stimulants than with α_2-adrenergic agonists.

In this study, clinicians were more likely to prescribe α_2-adrenergic agonist to younger children, which is consistent with other studies.[17,20] Although younger preschool-age children were not more likely to respond to α_2-adrenergic agonists than stimulants in this study, children younger than 4 years who were prescribed an α_2-adrenergic agonist were likely to continue receiving these medications longer than if they were prescribed a stimulant, suggesting that clinicians may judge the combined beneficial effects and adverse effects of α_2-adrenergic agonists more favorably than of stimulants for the youngest preschool-age children. In contrast, children aged 5 to younger than 6 years prescribed a stimulant were likely to continue receiving these medications for a longer time than α_2-adrenergic agonists. Given this study's retrospective design, the magnitude of the improvement was only quantified as "much improved" or "very much improved." The severity of the adverse effects was not categorized and the clinician's reasoning when changing medications was unknown. Thus, it is not possible to know whether the magnitude of the beneficial effect, severity of adverse effects, different time course for medications, or other factors influenced decisions to stop a medication.

This study has several strengths, including the large and diverse sample from multiple sites in different geographic locations in the US and the excellent interrater agreement on abstraction.

Limitations

This study has several limitations. First, the retrospective medical record review methodology did not enable data collection on magnitude or time course of the benefit and severity of the adverse effects or baseline severity of ADHD symptoms. Second, primary data entry into the medical records was not standardized, although data abstraction from the medical records was standardized. The retrospective nature of this study did not permit direct assessment of the effect of confounding factors, such as clinician preference and comorbid conditions, on initial medication prescribed. Third, initial ADHD medication selection might be influenced by confounding factors, such as coexisting conditions, that also affect the outcomes of this study; thus these findings are exploratory and a randomized clinical trial is needed to better evaluate this. Fourth, reported improvement in ADHD symptoms and adverse effects were evaluated based on their occurrence during any treatment episode occurring during an interval. This approach could have led to overestimation of benefits based on a short episode of improvement or overestimation of adverse effects due to a transient adverse effect. However, these definitions were applied equally to both classes of medication and thus would not explain medication differences. The similarity between the adverse effect data in this study and the data reported in PATS[7] suggests that the method of analysis used in this study provided reasonable estimates of these parameters. Fifth, the lack of random assignment to interventions limits conclusions about relative medication improvement. However, the evaluation of medication response in clinical practice has advantages for generalization. Sixth, the data were obtained from developmental-behavioral pediatric practices, thus these children with ADHD were referred for subspecialty ADHD care, and future studies should be conducted within primary care practices to enhance generalizability.

Conclusions

In this retrospective review of health records of preschool-age children with ADHD treated in developmental-behavioral pediatric practices, improvement was noted in the majority of children who initiated α_2-adrenergic agonists or stimulants, with differing adverse effect profiles between medication classes. Further research, including from randomized clinical trials, is needed to assess comparative effectiveness of α_2-adrenergic agonists vs stimulants.

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Correction: This article was corrected on October 5, 2021, because of an error in the Results and Table 1 that indicated that 309, rather than 225, children received behavioral therapy prior to the initiation of medication. The text and table now present the correct numbers of children.

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