Time to Stable Dose of Psychostimulants in Pediatric Patients With ADHD

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OBJECTIVES The prevalence of attention-deficit/hyperactivity disorder (ADHD) is increasing and psychostimulants are the pharmacological standard of care. Patients benefit most when there is efficient titration to a stable dose of medication as defined by maintaining that same dose for 6 months. The aims of this study were to describe time to stable dose in a cohort of children with ADHD and examine the impact of demographic factors.

METHODS A list of pediatric patients with a diagnosis of ADHD in the electronic health record was generated, and a retrospective chart review of stimulant use was conducted on 500 patients randomly selected from 2010 to 2015 who met inclusion criteria. Time to stable dosing and its association with demographic characteristics were assessed.

RESULTS Patients were predominantly male (72%), white (81%), and privately insured (67%). Fifty-five percent of patients achieved a stable dose of medication on first attempt; therefore, the median time to stable dosing for the cohort was 0 days with the interquartile range being 0 to 133.8 days. There was significant increase in time to stable dose for patients younger than 10 years compared with those ≥ 10 years of age ($p = 0.01$). Time to stable dose was not significantly associated with race ($p = 0.13$), sex ($p = 0.72$), type of insurance ($p = 0.56$), or formulation being immediate or extended release ($p = 0.56$).

CONCLUSIONS Many patients had long titration periods when trying to reach a stable dose. Given that medication switching can be challenging for patients and families, more frequent contact with providers during titration may be necessary.

ABBREVIATIONS ADD, attention deficit disorder; ADHD, attention-deficit/hyperactivity disorder; EHR, electronic health record; FDA, US Food and Drug Administration; ICD, International Classification of Diseases; IQR, interquartile range

KEYWORDS attention-deficit/hyperactivity disorder; behavior; pediatrics; psychostimulants; therapeutics

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common childhood behavioral disorder and has been diagnosed in approximately 9.4% of children (6.1 million) aged 2 to 17 years in the United States.^{1,2} The prevalence rate has increased 42% from 2003 to 2011.³ The annual national direct and indirect cost of ADHD ranges from \$143 billion to \$266 billion, with over 50% of the burden from expenses such as treatment costs and workday loss for parents.^{4,5}

Pharmacotherapy is demonstrated to be successful in treating this condition, and an estimated 62% of children with ADHD take medication.⁶ Psychostimulants are considered the pharmacological standard of care for symptoms, and, given their consistent efficacy and cost effectiveness, their use increased 28% in children aged 14 to 17 years from 2007 to 2011.³

Patients benefit most when medication is efficiently titrated to a stable dose. Given this, physicians take a

number of approaches in an effort to reach stable dosing efficiently. These approaches include prescribe and wait, dose-to-improvement, forced-dose titration, and blinded placebo trials. The prescribe-and-wait method is the most common.⁷ During this titration process, patient treatment adherence and physician contact play a key role in successful stimulant treatment. However, there is minimal research on the duration of titration.

The primary aim of this study was to describe time to stable dose in a cohort of ADHD patients treated at community pediatric practices of a large urban hospital system. Secondary aims were to examine the association of age at treatment initiation, sex, race, type of insurance, and medication formulation on the time to stable dosing. We hypothesize that time to stable dosing will be at least 3 months, based on improvement in ADHD symptomatology with stimulant treatment as previously described by Epstein et al.⁸ Additionally, we hypothesize that time to stable dosing will be longer in younger children, as defined by <10 years old, and in non-white populations.^{9–13}

Figure. Study participant selection process.

ADD, attention deficit disorder; ADHD, attention-deficit/hyperactivity disorder; CCF, Cleveland Clinic Foundation; ICD, International Classification of Diseases.

Materials and Methods

Study Population. A list of all pediatric patients with an International Classification of Diseases (ICD)-9 or ICD-10 diagnosis of ADHD and its subtypes in the electronic health record (EHR) system was generated and included 17,617 patients from urban, suburban, and rural centers. The list was randomized by using R software, and consecutive patients from the randomized list were assessed for inclusion in the chart review until a sample size of 500 subjects was selected. If a patient did not meet inclusion criteria, the patient was skipped; chart review continued until 500 patients were reviewed in total. All patients who were 6 to 15 years old anytime between the years 2010 to 2015 were included because 6 years is the earliest age for which most FDA-approved psychostimulants are indicated. Patients 16 years and older were considered adults and not included. Other inclusion criteria consisted in patients having at least 3 years of EHR data total; this could be any type of documentation, not just ADHD-related data. Patients could not be on stimulant medication prior to their first encounter for ADHD. They also had to be managed by physicians practicing at the community pediatric practices.

Patients were excluded if they never reached a stable dose, meaning that they never completed a 6-month period with the same medication. Those whose stimulant prescriptions were eventually managed by providers outside of the system within the first 2 years of therapy initiation or whose medication was managed by a pediatric subspecialist (i.e., neurologist, developmental pediatrician, psychiatrist) were excluded (Figure).

Study Design. A retrospective chart review was

conducted on the 500 selected patients who met the inclusion criteria described above. Time to stable dosing was defined as maintaining a prescribed dose for at least 6 months. Six months was chosen as the time to stable dosing, based on prior recommendations that once patients reach symptom improvement, they should be maintained on that dose for at least 6 months.¹⁴ Patients were considered to have reached a stable dose as long as they did not go off medication for more than 1 month during the 6-month period. This 1-month window was allotted to account for situations such as insurance changes. Patients were also considered to have reached stable dosing even in the event that an afternoon “sculpted” (or a small booster dose of a short-acting stimulant) medication was added, as long as the primary stimulant medication dose did not change. Addition of a “booster” was permitted because it was not considered to be responsible for the patient’s major symptom changes and was not reflective of inadequate treatment by the primary stimulant, but rather fulfilled the need to prolong the duration of an otherwise effective medication. Time to stable dosing was calculated from the patient’s first visit between 2010 and 2015 up until their most recent prescription. This allowed for examination of time to stable dosing at any point after the initial visit that occurred sometime between 2010 and 2015.

Data were abstracted via manual chart review of the EHR and documented and managed with REDCap. Data collected related to demographics and medication formulation as follows: sex, age, race, insurance type, specific ADHD diagnosis, comorbid psychiatric conditions, and medication formulation, either immediate or extended release (Table 1). Age was dichotomized

Table 1. Demographic Characteristics of the Pediatric ADHD Population (N = 500)

Demographic	Results
Male sex, n (%)	359 (71.8)
Age at first dose, yr, mean $\pm$ SD	9.3 $\pm$ 2.)
Race, n (%)	
White	405 (81)
Black	51 (10.2)
Other	24 (4.8)
Unavailable	20 (4)
Insurance, n (%)	
Private insurance	337 (67.4)
Public insurance	152 (30.4)
Self-pay	1 (0.2)
Unavailable	10 (2)
Primary diagnosis, n (%)	
ADHD inattentive (F90.0)	134 (27)
ADHD hyperactive (F91.1)	64 (12.8)
ADHD combined (F90.2)	123 (24.6)
ADHD other (F90.8)	1 (0.2)
ADHD unspecified (F90.9)	178 (35.6)
ADD without hyperactivity (314.00)	75 (15)
Comorbid psychiatric conditions, n (%)	
Anxiety	81 (16.2)
Depression	52 (10.4)
Substance abuse	3 (0.6)
Bipolar	6 (1.2)
Disordered eating	2 (0.4)
Obsessive compulsive disorder	8 (1.6)
Oppositional defiant disorder	26 (5.2)
Learning disability	23 (4.6)
Autism spectrum disorder	33 (6.6)
Schizophrenia or psychotic disorder	0 (0)
Other	11 (2.2)
None listed	310 (62)
Stimulant formulation, n (%)	
Immediate release	303 (60.6)
Extended release	192 (38.4)
Not documented	5 (1)

ADD, attention deficit disorder; ADHD, attention-deficit/hyperactivity disorder

into groups <10 years and $\geq$ 10 years. This was done because children younger than 10 years were predicted to have more difficulty adjusting to their medication dosage, based on clinical experience from physicians at the institution where this study was conducted. The division also allowed determining how time to stable

dosing differed among the younger and older members of the 6- to 15-year-old cohort.

Statistical Analysis. Categorical variables were reported as frequencies and proportions. Numeric variables were described by using means and standard deviations. Wilcoxon signed rank tests were used to

Table 2. Impact of Different Demographic and Medication Factors on Time to Stable Dose in a Pediatric Attention-Deficit/Hyperactivity Disorder Population

Demographic	No.	Time to Stable Dose, days, IQR	Maximum Time to Stable Dose, days	p value*
Overall	500	0–133.8	2282	
Age, yr				
<10	285	0–187.5	2282	0.1
≥10	215	0–78	1927	
Sex				
Male	359	0–121.7	2282	0.72
Female	141	0–182	1639	
Race†				
White	405	0–131.5	2282	0.13
Non-white	75	0–192.5	1146	
Insurance type‡				
Private	337	0–134.3	1927	0.56
Public	152	0–155	2282	
Formulation§				
Immediate release	303	0–125	1927	0.56
Extended release	192	0–159.8	2282	

* Wilcoxon signed rank test.

† Twenty patients with missing data.

‡ Ten patients with missing data.

§ Five patients with missing data.

analyze association between categorical variables and time to stable dose when the distribution was skewed. Medians, IQR, and maximum number of days to response are reported. Data were analyzed with JMP software (SAS Institute, Cary, NC).

Results

Of the 500 patients who met inclusion criteria, 72% (359/500) were male. Eighty-one percent ($n = 405$) of the patients were white, 10% ($n = 51$) were black, and 4.8% ($n = 24$) were identified as another race (labeled “other”). Sixty-seven percent ($n = 337$) of patients were privately insured and 30% ($n = 152$) had public insurance. The mean age at first dose was 9.3 ± 2.8 years (Table 1).

The most common diagnosis was unspecified ADHD (36%, $n = 178$), followed by ADHD inattentive type (27%, $n = 134$) and ADHD combined type (25%, $n = 123$). The remaining diagnoses were ADHD hyperactive type (13%, $n = 64$) and ADHD other (0.2%, $n = 1$). In the sample, 38% ($n = 190$) of the cohort were found to have a comorbid psychiatric condition. The most common was anxiety in 16% ($n = 81$) of the cohort. Other common comorbid conditions included depression (10%, $n = 52$) and autism spectrum disorder (7%, $n = 33$) (Table 1).

In this cohort of 500 patients, the median time to stable dosing was 0 days as defined by not changing the dose after the initial one was chosen. In all subgroup

analyses, the median time to stable dosing was also 0 days. There were 276 (55%) patients whose time to stable dosing was 0. For the cohort of 500 patients, the IQR for time to stable dosing was 0 to 133.8 days. The maximum was 2282 days (Table 2).

Patients younger than 10 years had an IQR for time to stable dose of 0 to 187.5 days, with a maximum of 2282 days. Patients 10 years and older had an IQR of 0 to 78 days with a maximum of 1927 days. There was a statistically significant greater time to stable dose for patients younger than 10 years at the time of the first prescription ($p = 0.01$).

Non-white patients had an IQR for time to stable dose of 0 to 192.5 days. The maximum was 1146 days. White patients had an IQR of 0 to 131.5 days with a maximum of 2282 days. There was a greater time to stable dose in non-white patients, though it was not statistically significant ($p = 0.13$). Female patients had an IQR to stable dose of 0 to 182 days, with a maximum of 1639 days, as compared with male patients who had an IQR of 0 to 121.7 days with a maximum of 2282 days. There was no significant difference in time to stable dosing by sex ($p = 0.72$).

Privately insured patients had an IQR of 0 to 134.3 days, with a maximum of 1927 days. Patients with public insurance had an IQR of 0 to 155 days with a maximum of 2282 days. There was no significant difference in time to stable dosing by insurance type ($p = 0.56$).

Patients prescribed an immediate-release formulation had an IQR of 0 to 125 days with a maximum of 1927 days. Patients administered extended-release formulations had an IQR of 0 to 159.8 days with a maximum of 2282 days. There was no significant difference in time to stable dosing whether the initial prescription was an immediate- or extended-release formulation ($p = 0.56$) (Table 2).

Discussion

Principal Findings. From this study of a cohort of patients diagnosed with ADHD and treated at community pediatric practices of a large urban hospital, 55% of pediatric patients achieved a stable dose of medication on the first attempt, with a quarter of patients requiring more than 130 days to reach stable dosing. The maximum time to reach a stable dose was several years. Our findings also show a significantly longer time to stable dose if a patient was younger than 10 years, with an IQR of 0 to 187.5, than for patients 10 years or older, with an IQR of 0 to 78 days. There is also a noticeably greater time to stable dose in non-white patients. This finding was not statistically significant but may be clinically significant because the non-white IQR was 0 to 192.5 days as compared with 0 to 131.5 days for white patients. This could contribute to additional frustration and extended suboptimal symptom control in the non-white population. There was no significant difference based on sex, type of insurance, or whether the formulation of medication was immediate or extended release.

Similarity of Our Cohort to the General ADHD Population. Across sex, age at diagnosis, comorbidities, and race, our sample had similarities to the general population of ADHD patients. In this cohort, there was a 2.5:1 male to female ratio among ADHD patients, which aligns with the 2–3:1 sex-based diagnosis ratios previously described.^{15,16} In terms of comorbidities, the National Survey of Children's Health found that ADHD patients were also diagnosed with anxiety, depression, autism spectrum disorder, and behavior or conduct problems, which were frequently present in our cohort as well.² For the types of ADHD, we did have a larger percentage of ADHD unspecified type when compared with the general population. We hypothesize this is an artifact of incomplete labeling in the EHR.

We found that the average age at first stimulant prescription for ADHD was 9.3 years, which aligns with prior findings that the average age of methylphenidate initiation is 8.7 years.¹⁷ Our cohort was predominantly white. This could in part reflect the lower rate of ADHD diagnosis in African American and Latino children than in white children.^{12,13} Overall, these comparisons demonstrate the potential applicability of our findings to other ADHD cohorts treated at community pediatric practices.

Primary Aim. One major study conducted by Epstein et al⁸ used parent and teacher versions of the Vanderbilt ADHD Rating Scales to track the timeline by

which ADHD symptomatology improved, and found it to be 3 months.^{8,18} Our finding that a quarter of patients required more than 130 days to reach stable dosing mirrored their findings. We recognize that symptom reduction and time to stable dosing are different variables; however, it is assumed that when stable dosing is reached there is some symptom reduction. One difference between our study and that of Epstein et al⁸ is that physicians in their study were previously trained on how to systematically implement the American Academy of Pediatrics management guidelines. Our study examined time to stable dosing when there was no physician training on the American Academy of Pediatrics guidelines, more closely reflecting actual clinical practice. Regardless, the amount of time it takes to achieve a stable dose and to improve ADHD symptoms is prolonged in 45% of patients, and strategies to reverse this trend must be devised.

Secondary Aims. Our findings that age <10 years is associated with longer time to stable dose is possibly due to the lack of breakdown of titration protocols based specifically on age. ADHD in young children is often treated by following research on what is efficacious and safe in older children and adolescents.^{9–11} This absence of data specifically for different age ranges, such as those younger than 10 years, may lead to prolonged time to stable dosing in this group. There is a growing body of information on preschooler and kindergarten treatment.^{19–21} However, further age breakdown may be needed regarding medication titration in children aged 6 to 10 years specifically. No research currently exists on how pharmacokinetics in this younger age group may also play a role and result in more difficult titration. Our finding that the non-white race cohort had a longer time to stable dose by more than a month is potentially explained by health care disparities and reduced physician contact in this population.

Racial/ethnic disparities with medication use for ADHD have been documented.^{12,13} It is hypothesized this is due to underdiagnosis and undertreatment of African American and Latino patients rather than overdiagnosis of white patients. It is known that physician contact and engagement/partnership with families play a major role in both medication adherence and improved ADHD medication titration.^{7,22} This supports the idea that more physician attention is needed in these populations.

Strengths and Limitations. The strengths of this study lie in the importance of addressing prolonged time to stable dosing in the care of pediatric patients with ADHD and the evaluation of possible mediators that influence ADHD medication management. Another strength of this study is that the cohort is representative of the broader ADHD patient population. Our data also capture routine practice across a large primary care network of 29 offices and 106 providers. Finally, bias was minimized by using a randomly generated subset of eligible patients.

Several limitations exist. First, data were extracted directly from the EHR to avoid recall bias; however, we acknowledge our assumption that the information within the EHR is accurate. We are further limited by the data available in the EHR, which allowed us to only measure time to stable dose. We recognize that stable dose may not mean optimal dose. In fact, our data show that 55% of patients achieved stable dosing immediately, which suggests they may have settled for symptom reduction and not optimal symptom control. Thus, truly optimizing a patient's treatment and then maintaining a stable dose of medication likely takes much longer, but we were not able to assess this. We did not take into consideration the specifics of the ADHD diagnosis, booster dosing, type of medication, or the weight of the child when calculating time to stable dosing. However, future studies could factor in these variables to see how they may affect time to stable dosing. Finally, we are not sure of the prescribing practices of the various physicians included in this study, as some may have had more training and experience. Future studies could look for time to stable dosing patterns compared between individual physicians.

Summary

Our retrospective chart review of a predominantly white, male, and privately insured ADHD pediatric population showed that in 45% of patients, a titration process to reach stable dosing would need to occur. This is not a short process; in 25% of patients it will take more than 4 months. Some patients may take years to reach a stable dose. This is an extensive period that can be frustrating for patients, parents, and physicians. This period delays symptom improvement and puts children at risk for poor academic performance, social challenges, family discord, risk-taking behavior, and low self-esteem. We found a significant increase in time to stable dosing for patients younger than 10 years and a longer time to stable dosing in non-white patients than white patients. Overall, given the extensive time to stable dosing, and the vulnerability of younger children and non-white patients to prolonged time to stabilization, it is critical that physicians maintain close contact with families when managing ADHD, especially during initiation and titration of stimulant medications.

Reassurance, support, and advocating for adherence may help to reduce time to stable dosing and achieve efficacious treatment of ADHD with stimulant medications more rapidly, resulting in a more positive impact on patients and families. Physicians should encourage their patients to schedule more appointments or make use of alternative touch points (e.g., phone, virtual visits, patient portal messages) during that initial titration phase. In addition, supplemental practitioners, such as pharmacists or nurse practitioners, may assist in those interim visits while titration is occurring, lowering cost and creating flexibility for families. These efforts may

help to reduce this currently prolonged time to stable dosing. Future studies comparing routine care to rapid titration models are warranted.

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Ethical Approval and Informed Consent Given the nature of this study, the project was exempt from institution review board/ethics committee review. HIPAA Waiver of Authorization, Waiver of Assent, and Waiver of Parental Permission were exempted.

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REFERENCES

1. Rostain A, Jensen PS, Connor DF, et al. Toward quality care in ADHD: defining the goals of treatment. *J Atten Disord.* 2015;19(2):99–117.
2. Danielson ML, Bitsko RH, Ghandour RM, et al. Prevalence of parent-reported ADHD diagnosis and associated treatment among U.S. children and adolescents. *J Clin Child Adolesc Psychol.* 2018;47(2):199–212.
3. Visser SN, Danielson ML, Bitsko RH, et al. Trends in the parent-report of health care provider diagnosed and medicated ADHD: United States, 2003–2011. *J Am Acad Child Adolesc Psychiatry.* 2014;53(1):34–46.
4. Le HH, Hodgkins P, Postma MJ, et al. Economic impact of childhood/adolescent ADHD in a European setting: the Netherlands as a reference case. *Eur Child Adolesc Psychiatry.* 2014;23(7):587–598.
5. Abright AR. Estimating the costs of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry.* 2012;51(10):987–989.
6. Garfield CF, Dorsey ER, Zhu S, et al. Trends in attention deficit hyperactivity disorder ambulatory diagnosis and medical treatment in the United States, 2000–2010. *Acad Pediatr.* 2012;12(2):110–116.
7. Manos MJ, Giuliano K, Geyer E. ADHD: overdiagnosed and overtreated, or misdiagnosed and mistreated? *Cleve Clin J Med.* 2017;84(11):873–880.

8. Epstein JN, Langberg JM, Lichtenstein PK, et al. Attention-deficit/hyperactivity disorder outcomes for children treated in community-based pediatric settings. *Arch Pediatr Adolesc Med*. 2010;164(2):160–165.
9. Bhang S-Y, Kwack YS, Joung Y-S, et al. Factors that affect the adherence to ADHD medications during a treatment continuation period in children and adolescents: a nationwide retrospective cohort study using Korean health insurance data from 2007 to 2011. *Psychiatry Investig*. 2017;14(2):158–165.
10. Vaughan BS, Kratochvil CJ. Pharmacotherapy of ADHD in young children. *Psychiatry (Edgmont)*. 2006;3(8):36–45.
11. Mayes SD, Crites DL, Bixler EO, et al. Methylphenidate and ADHD: influence of age, IQ and neurodevelopmental status. *Dev Med Child Neurol*. 1994;36(12):1099–1107.
12. Morgan PL, Staff J, Hillemeier MM, et al. Racial and ethnic disparities in ADHD diagnosis from kindergarten to eighth grade. *Pediatrics*. 2013;132(1):85–93.
13. Coker TR, Elliott MN, Toomey SL, et al. Racial and ethnic disparities in ADHD diagnosis and treatment. *Pediatrics*. 2016;138(3). doi:10.1542/peds.2016-0407.
14. Southammakosane C, Schmitz K. Pediatric psychopharmacology for treatment of ADHD, depression, and anxiety. *Pediatrics*. 2015;136(2):351–359.
15. Ramtekkar UP, Reiersen AM, Todorov AA, et al. Sex and age differences in attention-deficit/hyperactivity disorder symptoms and diagnoses: implications for DSM- V and ICD-11. *J Am Acad Child Adolesc Psychiatry*. 2010;49(3):217–228.
16. Cantwell DP. Attention deficit disorder: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry*. 1996;35(8):978–987.
17. Mannuzza S, Klein RG, Truong NL, et al. Age of methylphenidate treatment initiation in children with ADHD and later substance abuse: prospective follow-up into adulthood. *Am J Psychiatry*. 2008;165(5):604–609.
18. Wolraich ML, Lambert W, Doffing MA, et al. Psychometric properties of the Vanderbilt ADHD diagnostic parent rating scale in a referred population. *J Pediatr Psychol*. 2003;28(8):559–567.
19. Vitiello B, Lazzaretto D, Yershova K, et al. Pharmacotherapy of the preschool ADHD treatment study (PATS) children growing up. *J Am Acad Child Adolesc Psychiatry*. 2015;54(7):550–556.
20. Cohen NJ, Sullivan J, Minde K, et al. Evaluation of the relative effectiveness of methylphenidate and cognitive behavior modification in the treatment of kindergarten-aged hyperactive children. *J Abnorm Child Psychol*. 1981;9(1):43–54.
21. Chacko A, Pelham WE, Gnagy EM, et al. Stimulant medication effects in a summer treatment program among young children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2005;44(3):249–257.
22. Kerse N, Buetow S, Mainous AG, et al. Physician-patient relationship and medication compliance: a primary care investigation. *Ann Fam Med*. 2004;2(5):455–461.