Healthcare Costs Associated with Adverse Events During Treatment Episodes for Pediatric Attention-Deficit/Hyperactivity Disorder

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Introduction

- Attention-deficit/hyperactivity disorder (ADHD) is characterized by inattention, hyperactivity and impulsivity, and impairments in executive function, emotional regulation, and motivation[1]
- ADHD is one of the most prevalent neurodevelopmental disorders in the pediatric population in the United States (US), with approximately 7 million (11.4%) children aged 3–17 years old ever diagnosed as of 2022[2]
- Adverse events (AEs) are common in pediatric patients treated for ADHD, posing challenges in managing the disorder effectively[3]
- While the healthcare resource utilization and costs associated with AEs from a payer's perspective have previously been assessed among adults with ADHD, there is limited real-world evidence in the pediatric population[4]

OBJECTIVE

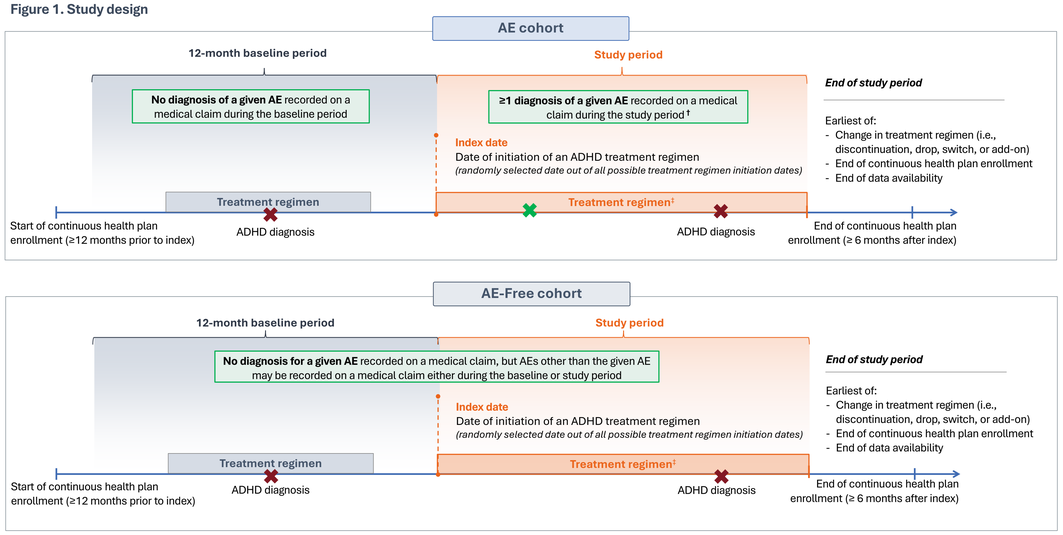
To evaluate the healthcare costs associated with common AEs among pediatric patients receiving treatment for ADHD in the US

Methods

Data source and study design

- A retrospective cohort study was conducted using the IQVIA PharMetrics® Plus database from October 1, 2015, to September 30, 2023
- Incremental healthcare costs associated with AEs during ADHD treatment episodes were assessed by comparing treatment episodes with a given AE to treatment episodes without the given AE (**Figure 1**)
- Studied AEs were selected based on statistically significant risk differences from a matching-adjusted indirect comparison (MAIC) of centanafadine and common pediatric ADHD treatments (i.e., lisdexamfetamine dimesylate, atomoxetine hydrochloride, viloxazine extended-release [ER], guanfacine ER, methylphenidate ER tablets and capsules)[5]
- Only AEs identifiable via International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes were considered for this analysis. Dry mouth was excluded due to small sample size.

Figure 1. Study design



† In addition to a given AE, other AEs may also be recorded on a medical claim during the study period.
‡ The treatment regimen initiated on the index date was defined as all ADHD-related agents with a prescription fill within 30 days after the index date.

Sample selection and study cohorts

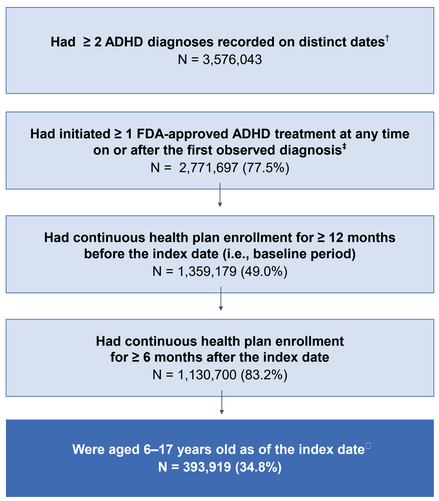
- Eligible pediatric patients were selected based on criteria detailed in **Figure 2**
- For each studied AE, patients were categorized into AE and AE-free cohorts based on the presence of ICD-10-CM codes for the given AE in medical claims
- Cohorts were not mutually exclusive across selected AEs: A patient could be included in the AE cohort for one AE (e.g., insomnia) while being in the AE-free cohort for another AE (e.g., vomiting)

AE cohort	AE-free cohort
Patients with ≥ 1 diagnosis for the given AE during the study period and no diagnosis for this AE during the baseline period	Patients with no diagnoses for the given AE during both the baseline and study period If the study period was shorter than 6 months, patients were required to have no AE during the first 6 months post-index date

Measures, outcomes, and statistical analyses

- Patient demographic and clinical characteristics were summarized descriptively
- AE and AE-free cohorts were reweighted using entropy balancing such that mean and standard deviation were similar across the following characteristics:
  - Age, sex, region, health plan type, calendar year of index date, line of therapy at index date, duration of index treatment regimen, pediatric comorbidity index score[6], specialist visits, and the number of other AE excluding the studied AE
- Healthcare costs were adjusted for inflation to the 2023 US dollar based on the medical component of the consumer price index and were reported from the payer's perspective (sum of the paid amount and coordination of benefits) as the average cost per-patient-per-month (PPPM)
- For each studied AE, a weighted two-part generalized linear regression model was used to compare healthcare costs between balanced AE and AE-free cohorts
  - **Total excess healthcare costs** included all-cause medical costs (i.e., inpatient, outpatient, and emergency room) and pharmacy costs (excluding ADHD treatment costs)
  - **AE-specific medical costs** included inpatient, outpatient, and emergency department medical costs for medical claims with a recorded diagnosis for a given AE
  - For example, for the vomiting cohort, only claims with a vomiting diagnosis were considered in AE-specific medical costs, while costs for potential complications (e.g., dehydration) were accounted for under total excess healthcare costs
- To contextualize the potential burden of AEs, annual AE-specific costs were estimated for a hypothetical health plan covering 1,000,000 pediatric members, while accounting for the prevalence of each AE

Figure 2. Sample selection flow chart



FDA: Food and Drug Administration
† ADHD was defined using the ICD-10-CM code F90.x
‡ Patients could have initiated more than 1 treatment (i.e., multiple candidate index dates). Treatment initiation occurring during inpatient stays were not considered.
ᵛ Only the variable year of birth is available in the IQVIA database. When determining patients' eligibility based on age (≥ 6 years old and < 18), all dates of birth were imputed as the mid-year point (July 1st).

Results

Patient characteristics and study cohorts

- A total of 393,919 pediatric patients were included (mean age: 12.5 years; male: 65.4%; stimulant monotherapy: 71.8%) (**Figure 3**)
- Overall, 13.6% had ≥ 1 studied AE during their treatment episode (**Figure 4**)
- The most prevalent AEs were upper abdominal pain (5.2%), vomiting (3.4%), and insomnia (3.2%) (**Figure 4**)

Figure 3. Patient characteristics

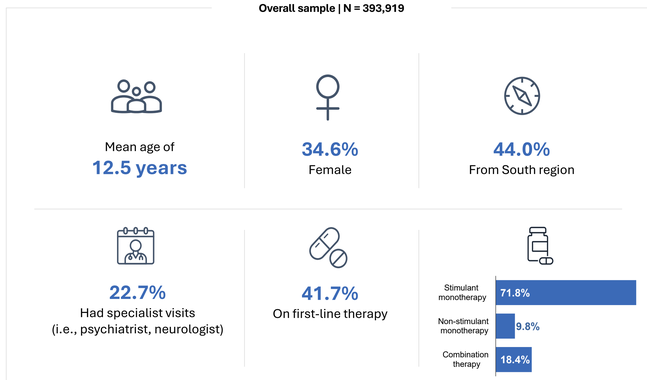
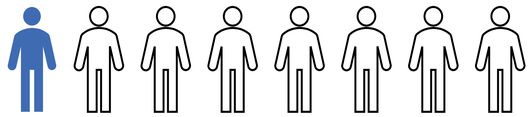
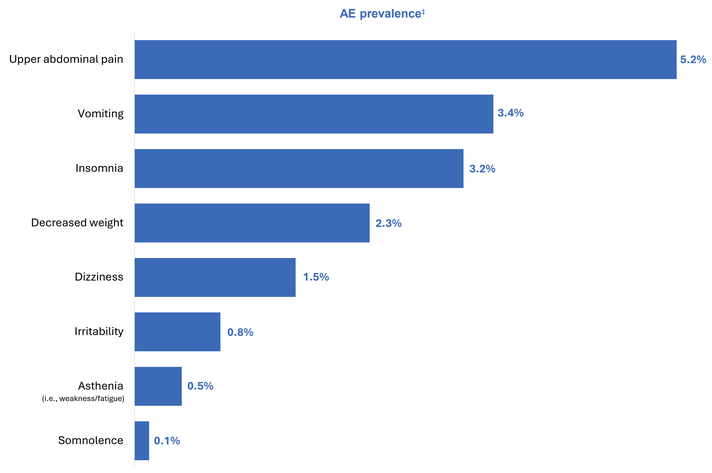


Figure 4. Prevalence of AEs during the study period



More than **1 in 8** patient had ≥ 1 AE during their treatment episode†

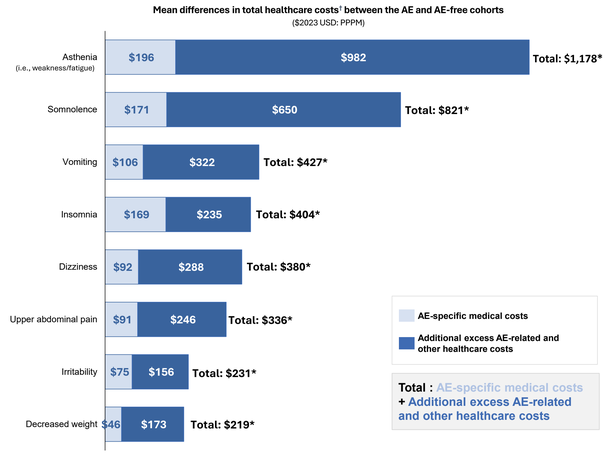


† AEs were identified based on recorded diagnosis on medical claims.
‡ Prevalence estimated from the proportion of patients with a diagnosis for a given AE recorded on a medical claim during their study period

Healthcare costs

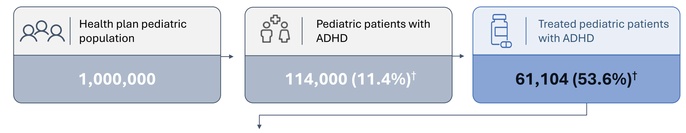
- All studied AEs were associated with statistically significant increased healthcare costs PPPM in the AE cohort compared with the AE-free cohort (all $p < 0.01$) (**Figure 5**)
- Total excess medical and non-ADHD treatment-related pharmacy costs were highest PPPM for: asthenia ($1,178), followed by somnolence ($821), vomiting ($427), and insomnia ($404)
- AE-specific costs were highest PPPM for: asthenia ($196), followed by somnolence ($171), insomnia ($169), and vomiting ($106)
- Healthcare costs associated with AEs can result in substantial expenditures for payers, particularly when factoring AE prevalence (**Figure 6**)
  - For example, although AE-specific medical costs associated with upper abdominal pain were $91 PPPM, when considering its prevalence (5.2%), this translates to nearly $3.5 million annually
  - Assuming each medical claim is associated to no more than one AE, a hypothetical plan covering 1 million pediatric members would incur annual costs of $13 million from medical claims for the 8 studied AEs among treated pediatric patients with ADHD

Figure 5. Incremental healthcare costs in the AE cohort compared to AE-free cohort (PPPM)



* Statistically significant at the < 0.01 level
† Additional excess AE-related and other healthcare costs exclude ADHD treatment-related pharmacy costs. All total healthcare cost differences were statistically significant at the 99% confidence level.

Figure 6. Estimated annual AE-specific medical costs in a hypothetical health plan with 1 million pediatric members



	AEs among treated pediatric patients with ADHD‡	Patient-level AE-specific medical costs during treatment episodes (per month)	Population level Total annual AE-specific medical costs in plan
Insomnia	1,929 (3.2%)	$169	$3,911,976
Upper abdominal pain	3,178 (5.2%)	$91	$3,456,959
Vomiting	2,104 (3.4%)	$106	$2,669,311
Dizziness	945 (1.5%)	$92	$1,047,873
Decreased weight	1,379 (2.3%)	$46	$757,064
Asthenia (i.e., weakness/fatigue)	277 (0.5%)	$196	$652,027
Irritability	504 (0.8%)	$75	$454,124
Somnolence	86 (0.1%)	$171	$175,891
Total annual AE-specific medical costs across all AEs in simulated health plan of 1,000,000 lives:			**$13,125,225**

† Assuming an ADHD prevalence of 11.4% and a treatment rate of 53.6% for non-institutionalized children aged 3–17 living in the US[2].
‡ Prevalence estimated from the proportion of patients with a diagnosis for a given AE recorded on a medical claim during their study period (based on total sample of 393,919 patients).
Note: Calculations are based on all AE-specific medical costs being independent – i.e., no more than one AE is recorded on an individual claim and AEs lasting for the entire 12-month period.
Example: vomiting had a prevalence of 3.4% in this study. In a hypothetical population of 1 million pediatric patients, this prevalence translates to 2,104 treated ADHD patients experiencing vomiting (3.4% of 61,104 patients). At the population level, the total annual AE-specific medical costs are: 2,104 treated ADHD patients experiencing vomiting x $106 AE-specific costs PPPM x 12 months = $2,669,311 (with rounding).

CONCLUSIONS

AEs were common during ADHD treatment episodes in pediatric patients and were associated with substantial all-cause and AE-specific healthcare costs

Findings highlight potential benefits of ADHD treatments with a favorable safety profile in reducing the burden of AEs on both patients and the healthcare system

Limitations

- Claims data limitations include the risk of data omissions, coding errors, and the presence of rule-out diagnosis, which may have led to the misclassification of patients in a given cohort
- This study captured AEs for which medical care was sought; as a result, milder AEs may be underrepresented. Additionally, it is not possible to determine whether AEs are treatment-related
- Cohorts were balanced on observable characteristics; residual confounding due to unobservable variables may still be present
- Results from this retrospective observational study should be interpreted as measures of association; no causal inferences can be made
- The study only included commercially insured patients, limiting the generalizability to the broader US pediatric ADHD population.

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Disclosures

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