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Vulnerabilities to antiepileptic drug (AED) side effects in youth with epilepsy

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ABSTRACT

Objective: The objective of the study was to investigate the relationship between sociodemographic, seizure-related, behavioral health, and antiepileptic drug (AED) adverse effect variables. The aim of this study was to examine whether there were significant differences on AED adverse effects between youth with normative and subclinical/clinical depressive and/or anxiety symptoms.
Methods: As part of a larger multisite validation study, 231 youth age 5 to 18 years diagnosed with epilepsy and their caregivers were recruited to participate for the current study. Youth ages 8 and older and caregivers of all youth completed the Behavior Assessment System for Children-2 (BASC-2). Caregivers also completed the Pediatric Epilepsy Side Effects Questionnaire (PESQ) and a Background Questionnaire. Medical chart review provided information regarding epilepsy diagnosis and treatment.
Results: No differences were observed in the mean scores on AED adverse effects between the group with subclinical/clinical BASC-2 Depressive symptoms and those with average/low depressive symptoms. In contrast, the proportion of youth with subclinical/clinical versus average/low depressive symptoms via caregiver report was significantly different for the cognitive, behavioral, general neurological, and total scale of the PESQ. There was also a larger proportion of youth with self-reported subclinical/clinical depressive symptoms who experienced general neurological adverse effects compared with youth with average/low depressive symptoms who experienced general neurological adverse effects. Findings were consistent for anxiety symptoms.
Significance: Identifying potentially modifiable behavioral health symptoms that exacerbate the expression of AED adverse effects could provide alternative solutions for improved AED tolerability to achieve optimum treatment outcomes.

1. Introduction

Antiepileptic drugs (AEDs) are the most common treatment for pediatric epilepsy; however, AED-related adverse effects continue to pose physical and behavioral challenges to youth with epilepsy and their families [1] and are associated with poorer health-related quality of life (HRQOL) [2]. A recent study has shown that youth with medically refractory epilepsy and/or a history of a behavioral health diagnosis are more likely to develop psychiatric or behavioral adverse effects related to AEDs [3]. Similarly, results in youth with new-onset epilepsy have shown that higher hyperactivity/impulsivity at baseline predicts greater behavioral AED adverse effects at one month post-AED initiation [4]. Adult studies have also shown that comorbid behavioral health symptoms can worsen the severity of adverse effects associated with AEDs [5,6] and that these behavioral health comorbidities are associated with poorer adherence to the prescribed AED regimen [7]. More specifically, Kanner and colleagues' [6] compared the effect of anxiety and depressive disorders as well as subclinical depressive episodes on AED-related adverse effects in adults and found that depression and anxiety worsen AED adverse effects even when presenting as subclinical symptoms.

Therefore, it appears that complex relationships between mood, behavior, seizures, and AED use may create challenges for epilepsy healthcare providers in treating seizures and comorbid behavioral health symptoms. Sociodemographic variables can also play an important role in AED use. Previous pediatric studies have revealed socioeconomic status (SES) as the sole significant predictor of AED adherence trajectories [8,9]. These studies point to the significance of consideration

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of sociodemographic variables when looking at AED use and adverse effects.

Providers and families must balance AED efficacy with adverse effects and HRQOL. However, few studies have addressed the relationship among AED adverse effects, sociodemographic variables, and comorbid behavioral health symptoms in children and adolescents with epilepsy, which are quite high with rates between 17 and 60% for anxiety and 8–25% for depression [10–12]. Further, existing studies have utilized non-standardized adverse effects data collection [3] or focused on specific subgroups (e.g., new-onset) [4]. Thus, results are not generalizable to youth on polytherapy or those with chronic AED use [13].

Examining the relationship between depressive and anxiety symptoms and adverse effects, in the context of multiple developmental processes in youth with epilepsy, may provide insight into how to treat epilepsy and its comorbidities in the pediatric population and ultimately improve healthcare outcomes, including HRQOL, and reduced healthcare costs [14]. Extending Kanner and colleagues' 2012 [6] approach with adults to pediatrics, our aim was to examine the potential relationships of depressive and anxiety symptoms per caregiver and youth report with AED adverse effects. Specifically, youth with clinical depressive and/or anxiety symptoms were hypothesized to report more severe adverse effects than youth with subclinical or normative depressive and/or anxiety symptoms.

2. Methods

2.1. Participants

Children and adolescents, age 8–18 years, further referred to as youth, and their caregivers participated in a larger multisite study [15] and were recruited from three pediatric epilepsy centers (Cincinnati Children's Hospital Medical Center (CCHMC), Children's Hospital of Orange County (CHOC), and Medical University of South Carolina (MUSC)). Inclusion/exclusion criteria for youth participants included the following: diagnosis of epilepsy, ability to read in English, and no other chronic medical condition, except for allergies and neurobehavioral comorbidities. The inclusion criteria for caregivers of youth included English fluency. Inclusion/exclusion criteria were both verified using participants' electronic medical records and healthcare providers.

2.2. Measures

Youth (ages 8 and older) who were able to self-report and their caregivers were asked to complete the Behavior Assessment System for Children-2 (BASC-2) [16]. The BASC-2 has been used extensively in youth with epilepsy and has shown exemplary psychometric properties including internal consistency, test–retest reliability, and construct validity [4,17]. Although the BASC-2 does not provide a diagnosis of depression or anxiety, many of the items on the Depression and Anxiety subscales address traditional symptoms of clinical depression from the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [18], and the BASC-2 is well respected as a quantified index of depressive and anxiety symptom severity [16]. In the current study, only the Anxiety and Depression subscales were used. According to the BASC-2 manual [16], T-scores of 70 and above are considered "clinically significant" while T-scores of 60–69 are considered "at risk." In the current study, we used the categories "clinical" ($T \geq 70$), "subclinical" ($T = 60–69$), and "average/low" ($T < 60$).

Caregivers also completed the Pediatric Epilepsy Side Effects Questionnaire (PESQ). The PESQ is a 19-item caregiver questionnaire that measures the severity of AED adverse effects in pediatric patients across the epilepsy spectrum [19]. The PESQ includes 5 subscales — Cognitive, Motor, Behavioral, General Neurological, and Weight. Raw scores are converted to scaled scores, including a total adverse effects score. Reliability (test–retest, internal consistency) and construct validity of the PESQ have been reported [19], with recent data identifying norms for new-onset and chronic epilepsy subgroups [13]. One standard deviation above the mean ($SD = 15$) signifies "high" adverse effects. For the purposes of the current study, the means and standard deviations from the mixed epilepsy sample (chronic and new-onset [13]) were utilized to determine boundaries for "high" versus "average" AED adverse effects.

Caregivers also completed a background questionnaire, which provided information regarding the youth's age, hospitalizations, comorbid diagnoses, and caregiver work history. The Revised Duncan score (range: 15–97) was calculated for each family based on caregiver occupation and serves as a measure of SES, with higher scores indicating higher SES [20]. Medical chart review revealed information regarding epilepsy type, treatment, seizure frequency in the past three months, and medical and psychosocial comorbidities.

2.3. Procedure

Participants were recruited by research personnel during an epilepsy visit (outpatient clinic, inpatient, and epilepsy monitoring unit) at the three sites, and informed consent from caregivers and assent from youth were obtained in accordance with the established methods of the Institutional Review Board. As part of the consent process, families were informed that they would receive modest compensation (gift cards) for their time. The study protocol was approved by each site's Institutional Review Board. Youth and caregivers completed study questionnaires during their epilepsy visit. Youth considered cognitively impaired by caregivers or their healthcare providers did not complete self-report questionnaires. Medical chart review was conducted by trained research staff at each site. Data collection was conducted between August 2014 and March 2016.

2.4. Statistical analysis

Responses on the BASC-2 were initially classified into average/low ($T < 60$), subclinical ($T = 60–69$), and clinical ($T \geq 70+$) symptoms for the BASC-2 Anxiety and Depression subscales. The PESQ total score was dichotomized (high/low) based on established means and SDs [13]. However, the distribution of the BASC-2 scores was severely skewed with few youth exhibiting clinically elevated depressive or anxiety symptoms. Therefore, the subclinical and clinical BASC-2 symptom groups were combined into one group (subclinical/clinical; $T \geq 60$) for both the child and caregiver scores. This also supported our belief of behavioral health screening and need to identify subclinical symptoms prior to clinical impairment in the context of epilepsy treatment.

Data analyses were conducted using the Statistical Analysis Software software package 9.4 [21]. Given the skewness of PESQ scores, i.e., over-representation of zeros (zero-inflated data), a dichotomous variable was created reflecting zero PESQ scores versus nonzero scores. Subsequently, to determine whether youth with subclinical or clinical depressive and/or anxiety symptoms reported more severe adverse effects than youth with normative depressive symptoms, nonparametric statistics (Wilcoxon Rank sum test, Chi-square test) were used to compare the nonzero and the binary PESQ scores respectively on both parent and youth BASC-2 scores (subclinical/clinical vs average/low symptoms). The severe skewness of the data precluded analyses using regression modeling.

3. Results

Two hundred and thirty-one caregivers and their youth with epilepsy age 8–18 years participated in the study (93 from CCHMC, 76 from CHOC, and 62 from MUSC). Approximately 65% of youth identified as White, non-Hispanic, and 54% were female. The majority of caregivers were married, and 61% had private insurance.

Thirty-eight percent had generalized epilepsy, and 53.5% experienced at least one seizure in the past three months. Seventy-eight percent were on monotherapy. The most commonly prescribed AED was

levetiracetam (Keppra) (22.5%), followed by valproate/Depakote/Depakene (18.4%). According to the background questionnaire, 25% percent of youth had a history of anxiety, and 11% had a history of depression. Youth who experienced AED adverse effects were younger, had lower SES, longer epilepsy duration, parents who were divorced, and were more likely to be on polytherapy compared with youth who did not experience AED adverse effects (see Table 1).

Two hundred and one caregivers (80 from CCHMC, 63 from CHOC, and 58 from MUSC) and 122 youth completed behavior rating scales. Responses on the BASC-2 indicated that 12% of youth (caregiver report) and 6% of youth (self-report) were experiencing clinical depressive symptoms (BASC-2 Depression subscale T ≥ 70+), with an additional 13% (caregiver report) and 10% (self-report) reporting subclinical symptoms (T = 60–69). Similarly, 7% of youth (caregiver report) and

Table 1
Sociodemographic and seizure variables by experiencing vs not experiencing antiepileptic (AED) drug total adverse effects (N = 231).

Variable	Total side effects			p-Value
	Total sample	No (n = 257)	Yes (n = 70)	
Age (years)	11.8 ± 3.6	12.1 ± 3.5	10.6 ± 3.9	**0.003**[a]
Race/ethnicity				0.105
White, not Hispanic	64.5% (149/231)	63.9% (117/183)	66.7% (32/48)	
Black, not Hispanic	13.9% (32/231)	12.0% (22/183)	20.8% (10/48)	
Other	21.7% (50/231)	24.0% (44/183)	12.5% (6/48)	
Sex				0.510
Female	54.1% (125/231)	53.0% (97/183)	58.3% (28/48)	
Male	45.9% (106/231)	47.0% (86/183)	41.7% (20/48)	
Marital status (Dad)[b]				**0.044**
Married	76.2% (138/181)	79.2% (118/149)	62.5% (20/32)	
Not married	23.8% (43/181)	20.8% (31/149)	75% (12/32)	
Marital status (Mom)[b]				**0.009**
Married	70.5% (146/207)	74.9% (122/163)	54.6% (24/44)	
Not married	29.5% (61/207)	25.2% (41/163)	45.5% (20/44)	
Insurance[b]				0.300[c]
Private	60.5% (135/223)	63.3% (112/177)	50.0% (23/46)	
Medicaid/public	37.2% (83/223)	34.5% (61/177)	47.8% (22/46)	
Both	1.8% (4/223)	1.7% (3/177)	2.2% (1/46)	
Not insured	0.5% (1/223)	0.6% (1/177)	0	
Highest family Duncan score (SES)[d]	57.1 ± 21.1	60.1 ± 20.6	46.1 ± 19.7	**0.0002**
Years since diagnosis	4.5 ± 3.9	4.3 ± 3.8	5.6 ± 4.2	**0.011**[a]
Epilepsy type				**0.014**
Localization-related/focal	46.8% (108/231)	48.6% (89/183)	39.6% (19/48)	
Generalized	37.7% (87/231)	39.3% (72/183)	31.3% (15/48)	
Localization-related vs generalized	15.6% (36/231)	12.0% (22/183)	29.2% (14/48)	
Onset				**0.032**
New-onset or 2 years or less	32.2% (74/230)	35.5% (65/183)	19.2% (9/47)	
More than 2 years	67.8% (156/230)	64.5% (118/183)	80.9% (38/47)	
Seizure control (no)[b]	53.5% (123/230)	50.3% (92/183)	66.0% (31/47)	**0.055**
Monotherapy (vs poly)[b]	78.3% (177/226)	84.9% (152/179)	53.2% (25/47)	<**0.001**
Number of AEDs[b]				<**0.001**[c]
0	1.7% (4/230)	1.7% (3/182)	2.1% (1/48)	
1	77.0% (177/230)	83.5% (152/182)	52.1% (25/48)	
2	15.2% (35/230)	11.0% (20/182)	31.3% (15/48)	
3	5.7% (13/230)	3.3% (6/182)	14.6% (7/48)	
4	0.4% (1/230)	0.6% (1/182)	0	
AEDs[e]				–
Carbamazepine/Tegretol or Carbatrol	6.7% (21/316)	6.0% (19/232)	0.6% (2/84)	
Clobazam/ONFI	5.4% (17/316)	2.5% (8/232)	2.8% (9/84)	
Clonazepam/Klonipin	1.3% (4/316)	0.6% (2/232)	0.6% (2/84)	
Diazepam/Diastat	7.9% (25/316)	5.7% (18/232)	2.2% (7/84)	
Ethosuximide/Zarontin	6.0% (19/316)	4.7% (15/232)	1.3% (4/84)	
Felbamate/Felbatol	4.4% (14/316)	2.2% (7/232)	2.2% (7/84)	
Lacosamide/Vimpat	3.2% (10/316)	2.2% (7/232)	0.9% (3/84)	
Lamotrigine/Lamictal	6.7% (21/316)	4.1% (13/232)	2.5% (8/84)	
Levetiracetam/Keppra	22.5% (71/316)	19.9% (63/232)	2.5% (8/84)	
Lorazepam/Xanax	0.3% (1/316)	0.3% (1/232)	0	
Midazolam/Versed	0.3% (1/316)	0.3% (1/232)	0	
Oxcarbazepine/Trileptal	8.2% (26/316)	7.3% (23/232)	0.9% (3/84)	
Phenytoin/Dilantin	0.3% (1/316)	0.3% (1/232)	0	
Rufinamide/Banzel	1.3% (4/316)	0	1.3% (4/84)	
Sodium Valproate	0.3% (1/316)	0.3% (1/232)	0	
Topiramate/Topamax	4.4% (14/316)	2.5% (8/232)	1.9% (6/84)	
Valproate/Depakote/Depakene	18.4% (58/316)	12.7% (40/232)	5.7% (18/84)	
Zonisamide/Zonegram	2.5% (8/316)	1.6% (5/232)	0.9% (3/84)	

Note:
[a] After log transformation.
[b] Inconsistencies due to missing data.
[c] From Fisher's Exact test.
[d] SES = socioeconomic status.
[e] Number/% of all AED occurrences across participants; some participants had more than one AED.

4% of youth (self-report) were experiencing clinical anxiety symptoms (BASC-2 Anxiety subscale T ≥ 70+), with an additional 17% (caregiver report) and 16% (self-report) experiencing subclinical symptoms (T = 60–69; see Table 2). Overall, caregivers reported that 24% of youth were experiencing subclinical to clinical depressive symptoms, and 30% were experiencing subclinical to clinical anxiety symptoms. Fifteen percent of youth reported subclinical to clinical depressive symptoms, and 18% reported subclinical to clinical anxiety symptoms. Agreement between youth and parent report of anxiety (kappa = 0.33, p = .0001) and depressive (kappa = 0.35, p = .0001) symptoms was fair.

We first examined differences between youth with average/low and youth with subclinical/clinical depressive symptoms on AED adverse effects. Differences were not observed in overall adverse effects scores between groups (see Table 2). In contrast, the percentages of absence versus experiencing adverse effects were statistically different between youth with average/low and youth with subclinical/clinical depressive symptoms, per caregiver report. For example, a higher percentage of youth with subclinical/clinical depressive symptoms experienced cognitive adverse effects compared with youth with depressive symptoms in the average/low (normative) range (p = .012). Similar findings were revealed for general neurological (p = .021), behavioral (p = .002) as well as total adverse effects (p = .010). A greater percentage of youth with self-reported depressive symptoms who experienced general neurological adverse effects was detected compared with youth without subclinical/clinical depressive symptoms who had general neurological adverse effects (p = .043).

Likewise, per caregiver report, more youths with subclinical/clinical anxiety symptoms had cognitive adverse effects compared with youth with normative anxiety symptoms (p = .040). Similar results were observed for total adverse effects (p = .034). There were also more youths with self-reported subclinical/clinical anxiety symptoms who experienced total adverse effects compared with youths with normative anxiety symptoms who experienced total adverse effects (p = .043) (Table 3).

4. Discussion

The aim of this study was to examine the relationship between AED adverse effects and sociodemographic and behavioral health variables in youth similar to Kanner and colleagues' [6] adult study. The overall mean for total AED adverse effects was low in this sample of mostly youth with chronic epilepsy (>2 years; 67.8%) on monotherapy. Junger and colleagues [13] examined means and standard deviations for the PESQ by chronic and new-onset epilepsy as well as mono- versus poly-AED therapy. In comparison with the means from the normative chronic monotherapy subgroup (5.20–11.86), the means for the current

Table 2
Comparison of antiepileptic drug adverse effect total and subscale mean scores by depressive symptom category as reported by parent and child. Frequencies, medians, and ranges for values above zero; frequencies and percentages for zero values (p-value from Wilcoxon Rank Sum test or Chi-square test, as appropriate).

Parent (N = 201)	BASC-2 Depressive symptoms		Wilcoxon/Chi-square
PESQ scale	Average/low (n = 151)	Subclinical or clinical (n = 50)	p-Value
Cognitive adverse effects	(n = 78) 30.0 (3.3–100)	(n = 36) 25.0 (3.3–86.7)	0.398
Yes	(n = 78) 51.7%	(n = 36) 72.0%	**0.012**
No	(n = 73) 48.3%	(n = 14) 28.0%	
Motor adverse effects	(n = 53) 15.0 (5–100)	(n = 23) 15.0 (5–75)	0.745
Yes	(n = 53) 35.1%	(n = 23) 56.0%	0.168
No	(n = 98) 64.9%	(n = 27) 54.0%	
General neurological adverse effects	(n = 77) 20.0 (5–85)	(n = 35) 30.0 (5–85)	**0.045**
Yes	(n = 77) 51.3%	(n = 35) 70.0%	**0.021**
No	(n = 73) 48.7%	(n = 15) 30.0%	
Weight adverse effects	(n = 47) 30.0 (10–100)	(n = 23) 40.0 (10–100)	0.475
Yes	(n = 47) 31.1%	(n = 23) 46.0%	0.056
No	(n = 104) 68.9%	(n = 27) 54.0%	
Behavioral adverse effects	(n = 52) 20.0 (6.7–100)	(n = 30) 30.0 (6.7–80)	0.107
Yes	(n = 52) 34.7%	(n = 30) 60.0%	**0.002**
No	(n = 98) 65.3%	(n = 20) 40.0%	
Total adverse effects	(n = 109) 11.6 (1.1–68.4)	(n = 45) 14.7 (2.1–77.9)	0.202
Yes	(n = 109) 72.2%	(n = 45) 90.0%	**0.010**
No	(n = 42) 27.8%	(n = 5) 10.0%	
Child (N = 122)	**BASC-2 Depressive symptoms**		**Wilcoxon/Chi-square**
PESQ scale	Average/low (n = 103)	Subclinical or clinical (n = 19)	p-Value
Cognitive adverse effects	(n = 53) 23.3 (3.3–83.3)	(n = 13) 33.3 (3.3–50)	0.994
Yes	(n = 53) 51.5%	(n = 13) 68.4%	0.173
No	(n = 50) 48.5%	(n = 6) 31.6%	
Motor adverse effects	(n = 28) 15.0 (5–75)	(n = 9) 10.0 (5–25)	0.213
Yes	(n = 28) 27.2%	(n = 9) 47.4%	0.079
No	(n = 75) 72.8%	(n = 10) 52.6%	
General neurological adverse effects	(n = 55) 20.0 (5–85)	(n = 15) 20.0 (5–55)	0.512
Yes	(n = 55) 53.9%	(n = 15) 78.9%	**0.043**
No	(n = 47) 46.1%	(n = 4) 21.1%	
Weight adverse effects	(n = 33) 20.0 (10–100)	(n = 7) 20.0 (10–60)	0.786
Yes	(n = 33) 32.0%	(n = 7) 36.8%	0.682
No	(n = 70) 68.0%	(n = 12) 63.2%	
Behavioral adverse effects	(n = 36) 20.0 (6.7–100)	(n = 9) 20.0 (6.7–60)	0.898
Yes	(n = 36) 35.3%	(n = 9) 47.4%	0.317
No	(n = 66) 64.7%	(n = 10) 52.6%	
Total adverse effects	(n = 81) 10.5 (1.1–73.7)	(n = 17) 13.7 (2.1–34.7)	0.234
Yes	(n = 81) 78.6%	(n = 17) 89.5%	
No	(n = 22) 21.4%	(n = 2) 10.5%	0.275

Note:
PESQ = Pediatric Epilepsy Side Effects Questionnaire.
BASC-2 = Behavior Assessment Scale for Children-2nd Edition.

Table 3
Comparison of antiepileptic drug adverse effect total and subscale mean scores by anxiety symptom category as reported by parent and child. Frequencies, medians, and ranges for values above zero; frequencies and percentages for zero values (p-value from Wilcoxon Rank Sum test or Chi-square test, as appropriate).

Parent (N = 201)	BASC-2 Anxiety symptoms		Wilcoxon/Chi-square
PESQ scale	Average/low (n = 152)	Subclinical or clinical (n = 49)	p-Value
Cognitive adverse effects	(n = 80) 28.3 (3.3–100)	(n = 34) 26.7 (3.3–83.3)	0.858
Yes	(n = 80) 52.6%	(n = 34) 69.4%	**0.040**
No	(n = 72) 47.4%	(n = 15) 30.6%	
Motor adverse effects	(n = 57) 15.0 (5–100)	(n = 19) 25.0 (5–75)	0.690
Yes	(n = 57) 37.5%	(n = 19) 38.8%	0.873
No	(n = 95) 62.5%	(n = 30) 61.2%	
General neurological adverse effects	(n = 80) 22.5 (5–85)	(n = 32) 22.5 (5–65)	0.992
Yes	(n = 80) 53.0%	(n = 32) 65.3%	0.131
No	(n = 71) 47.0%	(n = 17) 34.7%	
Weight adverse effects	(n = 50) 40.0 (10–100)	(n = 20) 20.0 (10–100)	0.713
Yes	(n = 50) 32.9%	(n = 20) 40.8%	0.312
No	(n = 102) 67.1%	(n = 29) 59.2%	
Behavioral adverse effects	(n = 57) 26.7 (6.7–100)	(n = 25) 20.0 (6.7–60)	0.199
Yes	(n = 57) 37.7%	(n = 25) 51.0%	0.101
No	(n = 94) 62.3%	(n = 24) 49.0%	
Total adverse effects	(n = 111) 11.6 (1.1–77.9)	(n = 43) 12.6 (2.1–73.7)	0.548
Yes	(n = 111) 73.0%	(n = 43) 87.8%	**0.034**
No	(n = 41) 27.0%	(n = 6) 12.2%	
Child (N = 122)	BASC-2 Anxiety symptoms		Wilcoxon/Chi-square
PESQ scale	Average/low (n = 98)	Subclinical or clinical(n = 24)	p-Value
Cognitive adverse effects	(n = 51) 30.0 (3.3–83.3)	(n = 15) 23.3 (3.3–83.3)	0.795
Yes	(n = 51) 52.0%	(n = 15) 62.5%	0.357
No	(n = 47) 48.0%	(n = 9) 37.5%	
Motor adverse effects	(n = 28) 10.0 (5–75)	(n = 9) 10.0 (5–70)	0.743
Yes	(n = 28) 28.6%	(n = 9) 37.5%	0.394
No	(n = 70) 71.4%	(n = 15) 62.5%	
General neurological adverse effects	(n = 53) 20.0 (5–65)	(n = 17) 20.0 (5–85)	0.293
Yes	(n = 53) 54.6%	(n = 17) 70.8%	0.150
No	(n = 44) 45.4%	(n = 7) 29.2%	
Weight adverse effects	(n = 30) 35.0 (10–100)	(n = 10) 20.0 (10–100)	0.312
Yes	(n = 30) 30.6%	(n = 10) 41.7%	0.301
No	(n = 68) 69.4%	(n = 14) 58.3%	
Behavioral adverse effects	(n = 35) 20.0 (6.7–100)	(n = 10) 20.0 (6.7–60)	0.934
Yes	(n = 35) 36.1%	(n = 10) 41.7%	0.612
No	(n = 62) 63.9%	(n = 14) 58.3%	
Total adverse effects	(n = 80) 9.5 (1.1–73.7)	(n = 18) 15.0 (2.1–61.1)	**0.043**
Yes	(n = 80) 81.6%	(n = 18) 75.0%	0.464
No	(n = 18) 18.4%	(n = 6) 25.0%	

Note:
PESQ = Pediatric Epilepsy Side Effects Questionnaire.
BASC-2 = Behavior Assessment Scale for Children-2nd Edition.

sample were somewhat higher across all adverse effects domains (11.6–20.8). In general, the adverse effects scores for the current study are within a similar range of scores reported in previous studies using the PESQ, and low adverse effects scores appear to be common in youth on AED monotherapy [11,13].

Because of the extreme positive skew (i.e., large number of zero adverse effects scores), we were unable to conduct regression analyses to examine behavioral health predictors of adverse effects in AEDs. However, findings from the current study revealed a greater percentage of youth, per caregiver report, with subclinical/clinical depressive symptoms who had adverse effects compared with youth with normative depressive symptoms who had adverse effects across cognitive, neurological, behavioral, and total adverse effects domains. Similar results were found in the neurological adverse effect domain per youth report of depressive symptoms. A greater percentage of youth with subclinical/clinical anxiety symptoms had adverse effects compared with youth with normative anxiety symptoms who had adverse effects across cognitive (caregiver and youth report) and total adverse effect domains (caregiver report). Eighty-one percent of those with high total adverse effects had chronic epilepsy. Therefore, our results suggest that a greater number of youth with subclinical to clinically significant behavioral health symptoms (anxiety or depression) have AED adverse effects. This is true for both caregiver and youth report of the youth's behavioral health symptoms in multiple domains of AED adverse effects.

Similar findings have been reported in the literature. For example, Kanner and colleagues [6] showed significant relationships between behavioral health/psychiatric symptoms and AED adverse effects in adults, more specifically, depression and anxiety were significant predictors of AED adverse effects. Similarly, Chen and colleagues [3], in a study of children age 2–18 years, found that both psychiatric diagnosis and failing two or more AEDs predicted greater psychiatric and behavioral AED adverse effects; however, they did not examine separate psychiatric diagnoses. Conversely, Guilfoyle and colleagues [4] revealed that neither depression nor anxiety symptoms predicted adverse effects (PESQ Behavioral subscale) in a clinical sample of adolescents with new-onset epilepsy; however, they used only the behavioral subscale of the PESQ, which assesses solely externalizing behaviors.

Methodology across studies has varied in how investigators have captured adverse effects, psychiatric symptoms, seizures, and sociodemographics, which likely contribute to differences in these study findings [22]. For example, some studies have utilized standardized parent/self-reported rating scales [4,6]; others have used medical chart review [3]. To assess psychiatric symptoms, DSM diagnoses [3,6] versus rating scale index of symptoms severity [4,23] have been used.

In the current study, the majority of youth had chronic, focal epilepsy, and more than half experienced poor seizure control compared with studies of clinical patients with new-onset epilepsy [4] who are more likely to have experienced fewer cumulative effects of a chronic brain disorder. Consideration of the informants is also important. In the current study, results differed somewhat between caregiver and youth report; however, cross-informant agreement was fair and consistent with reports in the extant literature [24]. Having both youth and caregiver reports provides a more comprehensive picture of behavioral health symptomatology, and caregiver and youth scores on behavioral functioning should be used complementary [25].

The sociodemographic characteristics of the current study participants are notable for several reasons. The sample identified as primarily White, non-Hispanic with private insurance, and married caregivers, suggesting that the majority of participants may have access to resources, including accessible healthcare, and other factors promoting resilience [26]. However, in the current study, a lower level of SES was associated with higher adverse effects. Previous pediatric studies have shown that SES was the sole significant predictor of AED adherence trajectories [8], and nonadherence has been associated with greater AED adverse effects [9]. Other studies have revealed that depressive symptoms predict adult AED nonadherence [7], and AED adverse effects affect several HRQOL domains [2]. Therefore, a complex relationship may exist among AED adverse effects, adherence, quality of life (QOL), SES, and depressive symptoms for persons with epilepsy.

It is critical to assess baseline behavioral health symptoms prior to initiation of AED so that providers can assess the presence of baseline symptoms to distinguish between exacerbations of premorbid symptoms versus new-onset concerns with AED treatment as the appropriate interventions may differ [4]. Data from the current study further support that youth should be continually screened for psychiatric/behavioral health comorbidities, especially those with high AED adverse effects [27]. Behavioral health screening provides the epilepsy healthcare providers with additional data to interpret the adverse effects scores. This integrated care model allows for an evidence-informed proactive approach to the initiation of interventions that have the potential to modify behavioral health symptoms, which in turn, may make adverse effects more tolerable. Indeed, interventions focused on enhancing adherence and HRQOL, along with reducing depressive symptoms, have been developed for youth with epilepsy with promising outcomes [28–30]. In addition, the provision of behavioral healthcare for enhancement of epilepsy self-management may lead to reduced epilepsy healthcare visits and medical costs [14,31].

4.1. Limitations

The primary limitations of this study include the lack of data on psychiatric medication usage (e.g., [6]). Further, the study did not use diagnostic interviews but relied on paper–pencil questionnaires. Another limitation was the use of categorical cut-points for the BASC-2 instead of continuous data; however, this reflects the typical use of the scales in clinical practice, and findings are therefore directly applicable to clinical care. Further, our data were severely skewed with only few youth reporting clinically elevated depressive or anxiety symptoms. We did not screen or formally assess for cognitive impairments; therefore, we did not identify youth with cognitive impairments who did not complete the self-report measures or look at differences in caregiver reports of behavioral health for youth with impairments versus those with typical intelligence. A final limitation is that we were unable to analyze whether certain AEDs had stronger or weaker relationships with the other sociodemographic and clinical variables. This study also had several strengths, including a large sample size, a nationally representative sample, use of validated measures, and included both parent and youth reports of behavioral health symptoms.

4.2. Conclusions

The current findings contribute to the pediatric epilepsy research in several ways. Consideration for and treatment of behavioral symptoms in a comprehensive epilepsy care approach may lead to a reduction in AED adverse effects while maximizing AED efficacy (i.e., patient can remain on polytherapy and tolerate mild adverse effects — such as a lower frustration threshold) and adherence (youth are more likely to take medications as prescribed when the adverse effects are tolerable). Such behavioral changes in both the epilepsy healthcare professional (behavioral health screening) and the patient/family (improved adherence and lower adverse effects) may lead to improved QOL and reduced epilepsy healthcare visits and medical costs [14,31]. Future research efforts should control for psychiatric medication usage, employ methods to obtain information on behavioral health diagnoses, and investigate other behavioral aspects of AED adverse effects (mood symptoms, anxieties, disruptive behavior).

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Declaration of Competing Interest

None of the authors has any conflict of interest to disclose.

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