Obesity and overweight as CAE comorbidities and differential drug response modifiers

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ABSTRACT

Objective: This study examined whether overweight and obesity are pretreatment comorbidities and predictors of short-term drug response in newly diagnosed untreated childhood absence epilepsy (CAE). We also examined whether dietary intake accounts for observed pretreatment body mass index (BMI) distribution.

Methods: Pretreatment height and weight were available for 445 of 446 participants in the NIH-funded CAE comparative effectiveness trial (NCT00088452). Twenty-four-hour dietary recalls were collected. Calculated BMI and dietary intake were standardized for age, sex, and race/ethnicity and compared to age-matched US population from the National Health and Nutrition Examination Survey (NHANES). Logistic regression models tested BMI as a predictor of treatment response. Pharmacokinetic variables were explored as contributors to differential drug response.

Results: After standardizing for demographic differences, children with CAE were more likely to be overweight (19.3% vs 13.8%; $p < 0.001$) or obese (14.5% vs 11.5%; $p < 0.001$) than NHANES controls. The combined prevalence of overweight and obesity was 33.8% in the CAE cohort and 25.3% among controls ($p < 0.001$). Mean daily energy intake (difference -79.5 kcal/day, $p = 0.04$) and daily carbohydrate intake (difference -10.7 g/day, $p = 0.04$) were lower in the CAE group than in NHANES controls. With increasing baseline BMI z score, the efficacy and effectiveness of ethosuximide and valproic acid over lamotrigine became more pronounced, despite no significant differences in drug exposure and trough levels.

Conclusions: Overweight and obesity are more prevalent in children with newly diagnosed CAE than in age-matched peers, despite lower caloric and carbohydrate intake. Baseline BMI may also predict differential drug response, which cannot be attributed to pharmacokinetic differences.

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GLOSSARY

AED = antiepileptic drug; **BMI** = body mass index; **CAE** = childhood absence epilepsy; **CDC** = Centers for Disease Control and Prevention; **CI** = confidence interval; **ETX** = ethosuximide; **FFF** = freedom from failure; **LTG** = lamotrigine; **NDSR** = Nutrition Data System for Research; **NHANES** = National Health and Nutrition Examination Survey; **OR** = odds ratio; **SES** = socioeconomic status; **SF** = seizure freedom; **THIN** = The Health Improvement Network; **VPA** = valproic acid.

Overweight and obesity are worldwide pediatric problems with increasing prevalence and adverse biological, mechanical, social, and psychological health consequences.^{1,2} Overweight and obesity are recognized as important modifiers of severity, treatment response, natural history, and prognosis for several chronic diseases.^{3,4} There is a paucity of data about the prevalence of preexisting overweight/obesity in people with epilepsy despite understanding that comorbidities inform disease pathophysiology and influence drug selection and self-management.⁵

The only relevant previous study compared 251 children (aged 2–18 years) with new-onset untreated epilepsy to a regional healthy control cohort ($n = 597$) and standardized data from the Centers for Disease Control and Prevention (CDC).⁶ This study identified an increased

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prevalence of obesity (19.9%) and overweight (18.7%) in children with epilepsy compared to regional healthy controls (13.7% and 14.7%, respectively).⁶ However, this study had important limitations, including a single-center design, diverse epilepsy syndromes and etiologies, a geographically restricted control cohort, and no information about dietary intake or drug response. The present study addresses these limitations by comparing the prevalence of overweight/obesity and pattern of dietary intake in a national multicenter cohort of newly diagnosed untreated children with childhood absence epilepsy (CAE)^{7,8} to a national control cohort.⁹ The CAE cohort served as the study population of a randomized double-blind comparative effectiveness trial, which provided the opportunity to examine the effect of these comorbidities on short-term drug response.⁷

METHODS Definitions. Overweight and obesity were defined relative to age- and sex-specific CDC percentile curves based on body mass index (BMI; kg/m²) calculated from measured baseline height and weight.¹⁰ Obesity and overweight were defined as BMI of ≥ 95 th percentile and ≥ 85 th but < 95 th percentile for age and sex, respectively.

Study population. The CAE study was a 32-center randomized double-blind trial comparing the 3 most commonly used medications. The detailed trial methodology was published previously.^{7,8} The participants fulfilled the International League Against Epilepsy criteria for CAE, were between 2.5 and 13 years of age at entry, were untreated, were newly diagnosed, and had a BMI less than the lower limit for the 99th percentile for age and sex. Enrollment was from 2004 to 2007.

Data collection. Height and weight data were collected during the baseline visit before initiation of any study medication. Nutrient variables were obtained through a 24-hour diet recall interview performed as close to the baseline visit as possible. The dietary intake data were collected and calculations were performed using Nutrition Data System for Research (NDSR) software versions 5.0, 2005, 2006, 2007, and 2008 (Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN). NDSR provides a complete nutrient profile for all foods in the database.^{11,12} The NDSR time-related database updates analytic data while maintaining nutrient profiles true to the version used for data collection.¹³

Control population. Control data were obtained from the National Health and Nutrition Examination Survey (NHANES), an ongoing nationally representative survey of noninstitutionalized civilians residing in the United States.⁹ This survey's detailed methodology, including target population and data collection methods, is published elsewhere.⁹ Briefly, for each 2-year cycle, an independent sample is obtained using a 4-stage probability sampling design, which includes sequential selection of the primary sampling units (i.e., individual counties), segments within the counties, dwelling units or households within

segments, and finally individuals within a household. Data are collected via in-home questionnaires followed by a standardized physical examination in a specially equipped mobile center.

The present study used data collected from children aged 2.5 to < 13 years participating in the 2005–2006 NHANES cycle. Children with BMI ≥ 99 th percentile for age and sex and postmenarche females were excluded so that the sample was comparable to the CAE cohort.

Standard protocol approvals, registrations, and patient consents. The CAE study was approved by the institutional review boards at all 32 sites. Written parental informed consent and, when appropriate, child assent was obtained from all participants. The trial was conducted under a US Food and Drug Administration IND# 69,185 and is listed at clinicaltrials.gov (identifier NCT00088452).

Study hypothesis. The primary hypothesis was that overweight/obesity is more prevalent in children with newly diagnosed CAE than in an age-matched control population. Secondary hypotheses were that differences in the prevalence of overweight/obesity would be associated with dietary intake variables and differential drug response. Although not prespecified in the CAE study, these hypotheses were formulated based on preliminary work by the same principal investigator.⁶

Outcome measures. The primary outcome measure was the proportion of children with overweight and obesity (individually and together) in the CAE and NHANES cohorts. Secondary outcomes included individual drug responses, defined as “freedom from failure” (FFF) and seizure freedom (SF) at the week 16–20 visit after treatment initiation in the CAE study.^{7,8} Predictor variables included BMI z scores, obesity and overweight status, and total daily intake of energy, carbohydrate, protein, fat, fiber, and micronutrients (calcium, sodium, iron, vitamins C and D) determined by baseline 24-hour diet recall.

Statistical methods. Prevalence and means of the relevant variables were calculated for the CAE and age-matched NHANES cohorts. Anthropometric data for children were transformed into age- and sex-specific z scores using the 2000 CDC Growth Reference data,¹⁰ and overweight/obesity status was determined using standard percentile-based cutoffs for pediatric populations. The percentages of energy intake from macronutrients were calculated based on total daily consumption of energy (kcal/day) and intake of protein, fat, and carbohydrates (g/day) derived from the 24-hour dietary recall.^{11,13}

To account for differences in the sex and race/ethnicity distribution of the CAE study participants compared to the age-matched US population, direct standardization of CAE estimates was performed. Race/ethnicity was classified into 4 groups: Hispanic, non-Hispanic white, non-Hispanic black, and non-Hispanic others. When stratified by sex, 8 sex/race/ethnicity strata were obtained. The proportion of age-matched US population in each of these 8 strata was calculated using NHANES data. These proportions were used to calculate weighted prevalence(s) and mean(s) using the CAE study cohort data. Analyses of NHANES data incorporated sample weights accounting for selection probability and nonresponse to produce unbiased population-level estimates.

Standardized estimates of proportions and means for each outcome obtained from the CAE data were compared to those derived from the NHANES sample. Differences between estimates derived from the 2 groups and their 95% confidence intervals (CIs) were calculated. Adjustment for maternal education as a proxy for socioeconomic status (SES) was also explored. Although p values for these differences were derived,¹⁴ we do not emphasize

statistical significance in this analysis given the very large sample size of the control population.

A series of multivariable logistic regression models were fitted to evaluate baseline overweight, obesity, BMI *z* score, and different dietary intake variables as predictors of short-term drug response (FFF and SF at the week 16–20 visit) in the CAE cohort after accounting for randomized assignment and demographic variables (significance level set at $p \leq 0.05$). The main effect models for each variable were used to identify predictors of response, regardless of assigned treatment. Models of interactions between assigned treatment and the clinical predictors were used to identify variables that modify risk of treatment failure on any specific treatment. All analyses were performed in Stata version 13.1 (StataCorp, College Station, TX).

To investigate whether pharmacokinetic variables contribute to differential drug response, model-based prediction of area under the concentration-time curve for total drug exposure and trough levels were compared for all 3 study drugs in children with CAE with ≥ 85 th and < 85 th BMI percentile for age/sex using nonparametric Wilcoxon test.

RESULTS Of 446 children enrolled in the CAE trial, 445 had complete anthropometric data and were included in the primary analysis of BMI and overweight/obesity status. Of these, 437 (98.0%) children with completed 24-hour dietary recall were included in the secondary analyses. Population-based estimates were generated using data from 2,079 age-matched NHANES participants who underwent the physical examination, 1,912 (92.0%) of whom also provided dietary information.

CAE, obesity/overweight, BMI, and dietary intake. There were no group differences in the mean height (126.4 cm vs 125.6 cm, $p = 0.36$), weight (28.7 kg vs 29.0 kg, $p = 0.60$), or BMI (17.4 kg/m² vs 17.5 kg/m², $p = 0.96$) between the CAE and NHANES cohorts. However, mean BMI *z* scores for age and sex were higher for the CAE group (0.52 vs 0.33, $p = 0.01$, table 1), and their distribution in the CAE cohort was shifted rightward compared to the standard normal distribution, with this shift being greater than that for the NHANES group ($p = 0.001$, figure 1). The prevalence of overweight children was higher in the CAE group (19.3%, 95% CI 15.6–23.1) than in the NHANES group (13.8%, 95% CI 11.4–16.2, $p < 0.001$), as was the prevalence of obese children (14.5%, 95% CI 10.5–18.5 vs 11.5%, 95% CI 8.8–14.3, $p < 0.001$). Adjustment for maternal education did not change these results (data not shown).

Regarding dietary intake, the mean daily energy intake was borderline lower in the CAE group than in the NHANES group (mean difference -79.5 kcal/day, 95% CI -155.5 to -3.5 , $p = 0.04$). Also, the total daily carbohydrate intake was lower in the CAE group (mean difference -10.7 g/day, 95% CI -20.9 to -0.6 , $p = 0.04$). No other statistically significant differences were noted (table e-1 on the *Neurology*[®] Web site at Neurology.org).

Table 1 Comparison of NHANES and CAE study data after direct sex and ethnicity standardization of the CAE study sample to the age-matched US population: Anthropometry and dietary components

Characteristic	NHANES prevalence or mean (95% CI)	CAE study prevalence or mean (95% CI)	Difference in prevalence or means (CAE – NHANES, 95% CI)	p Value
Anthropometry	n = 2,079	n = 445		
BMI <i>z</i> score for age and sex	0.33 (0.22–0.44)	0.52 (0.42–0.62)	0.19 (0.05 to 0.33)	0.01 ^a
Overweight, ^b %	13.8 (11.4–16.2)	19.3 (15.6–23.1)	5.5 (5.1 to 6.0)	<0.001 ^a
Obesity, ^c %	11.5 (8.8–14.3)	14.5 (10.5–18.5)	3.0 (2.5 to 3.5)	<0.001 ^a
Overweight and obese, %	25.3 (20.7–29.9)	33.8 (28.9–38.8)	8.5 (7.8 to 9.2)	<0.001 ^a
Energy	n = 1,912	n = 437		
Energy, kcal	1,842.2 (1,779.7–1,904.7)	1,762.7 (1,712.8–1,812.6)	-79.5 (-155.5 to -3.5)	0.040 ^a
Macronutrients				
Total protein, g	62.5 (59.7–65.2)	61.2 (59.1–63.3)	-1.3 (-4.6 to 2.0)	0.446
Total fat, g	68.4 (65.4–71.5)	64.9 (62.4–67.3)	-3.6 (-7.3 to 0.2)	0.061
Total carbohydrate, g	250.0 (242.3–257.7)	239.3 (232.0–246.5)	-10.7 (-20.9 to -0.6)	0.038 ^a
Calories from protein, %	13.7 (13.4–14.0)	14.1–(13.7–14.4)	0.3 (0.1 to 0.8)	0.127
Calories from fat, %	32.8 (32.3–33.4)	32.5 (31.9–33.2)	-0.3 (-1.2 to 0.5)	0.461
Calories from carbohydrates, %	54.7 (53.9–55.6)	54.6 (53.8–55.4)	-0.1 (-1.2 to 1.0)	0.856
Fiber, g	12.3 (11.6–13.0)	11.9 (11.5–12.4)	-0.4 (-1.2 to 0.5)	0.405

Abbreviations: BMI = body mass index; CAE = childhood absence epilepsy; CI = confidence interval; NHANES = National Health and Nutrition Examination Survey.

^a Significant value.

^b Overweight defined as BMI ≥ 85 th to < 95 th percentile for age and sex.

^c Obesity defined as BMI ≥ 95 th percentile for age and sex.

Figure 1 CAE and NHANES BMI z scores density plots

Density plot of body mass index (BMI) for age and sex z scores derived from kernel density estimates based on the childhood absence epilepsy (CAE) study cohort and the age-matched National Health and Nutrition Examination Survey (NHANES) participants overlaid against a standard normal curve. The Kolmogorov-Smirnov test for equality of the CAE and NHANES distributions indicates a significant difference ($p = 0.001$).

BMI, drug response, and pharmacokinetics. Overall, overweight/obesity status and BMI were not found to predict treatment response at the week 16–20 double-blind visit (data not shown). However, with increasing pretreatment BMI z score, the differential efficacy and effectiveness of valproic acid (VPA) and ethosuximide (ETX) over lamotrigine (LTG) became more pronounced (figure 2). Compared with nonobese children receiving ETX, obese children on ETX had higher odds of achieving FFF (odds ratio [OR] 2.75, 95% CI 1.01–7.46, $p = 0.047$) and obese children on VPA had higher odds of achieving SF (OR 4.89, 95% CI 1.08–22.11, $p = 0.040$), whereas both obese and nonobese children on LTG were significantly less likely to experience FFF and SF (table 2). Considering obese/overweight participants together, children on LTG were significantly less likely to experience FFF and SF than children on ETX who were not overweight/obese.

Pharmacokinetic data, including model-predicted drug exposure and trough levels, were available for 143/154 (92.9%), 135/146 (92.5%), and 136/146 (93.2%) children randomized to the ETX, LTG, and VPA arms, respectively. For all 3 study medications, the groups with and without available pharmacokinetic data were not statistically different regarding age, sex, and race/ethnicity. Comparison of exposure and trough levels between groups of children with CAE with ≥ 85 th and < 85 th BMI percentile revealed no significant differences (table 3).

DISCUSSION This study demonstrates that overweight and obesity are comorbidities of new-onset CAE. They fulfill the conventional definition of the term “comorbidity,” which is simultaneous presence of 2 or more diseases or conditions in the same individual more frequently than the chance expectation derived from an age-matched control cohort of apparently healthy peers.^{15,16}

In a previous study including children aged 2–18 years ($n = 251$) with new-onset untreated epilepsy, the prevalence of obesity (19.9%) and overweight (18.7%) in these children was higher than in regional healthy controls ($n = 597$, 13.7% and 14.7%, respectively).⁶ The cumulative probability and probability density plots showed both the epilepsy and the regional healthy control cohorts toward the right of the standard normal curve, indicating a high rate of obesity in these groups. However, whereas that study included children with diverse epilepsies, including those with structural or metabolic etiology, the CAE study cohort represents a homogenous population of children recruited from 32 centers across the United States. Furthermore, the NHANES dataset is a nationally representative sample of the US population compared to the regional cohort recruited from southwestern Ohio in the earlier study.^{6,7,9}

The CAE trial excluded children who had received any antiepileptic drug (AED) for > 7 days before randomization. Thus, the weight data in the CAE study are free from weight-related effects of AEDs, which confound the majority of data regarding distribution of weight and BMI in people with epilepsy¹⁷ and

Figure 2 Effectiveness and efficacy as function of BMI z scores

Model-estimated probability of freedom from failure (A) and seizure freedom (B) as a function of body mass index (BMI) z scores among patients randomized to receive valproic acid (VPA), ethosuximide (ETX), and lamotrigine (LTG).

potentially bias any cross-sectional data about distribution of weight/BMI in a treated epilepsy cohort.

There is a paucity of analogous data about the coexistence of baseline obesity and epilepsy. A retrospective study based on The Health Improvement Network (THIN) in the United Kingdom examined the incidence rates of seizures across different BMI levels in adults aged ≥ 18 years ($n = 141,974$) and found a nonsignificant modestly increased risk in the incidence of seizures in obese patients (rate ratio 1.7, 95% CI 0.7–3.9).¹⁸ Although this study supported the concept of epilepsy-obesity comorbidity, several issues limit its generalizability. The study cohort was selected from THIN based on availability of BMI data, and the included cohort was dissimilar to the excluded patients regarding age and sex composition. Misclassification of seizures was also a potential source of bias for the incidence rate estimates, and the confounding effects of AEDs on weight were not adjusted for in the analyses.¹⁸ Another retrospective

study compared adults aged ≥ 66 years with ($n = 1,843$) and without ($n = 1,023,376$) epilepsy from National Veterans Affairs databases to investigate risk factors for new-onset geriatric epilepsy.¹⁹ Among other predictors identified on multivariate regression, obesity was associated with lower odds of epilepsy (OR 0.74, 95% CI 0.62–0.87). Extensive differences in the population and methodology between this study and ours limit any meaningful comparisons.

The possible mechanism of biological interaction between obesity and epilepsy and any indication of causal directionality remain elusive. Body weight is determined by interplay among energy intake, metabolism, and expenditure. Each of these processes is complex and incompletely characterized. For example, energy consumption is a function of food security, access, and appetite; general health and metabolism determine the energy extraction efficiency of the human body; and energy expenditure is related to physical activity. These variables are not

Table 2 Freedom from failure and seizure freedom for intersection of study drug with obese/overweight status at week 16–20 double-blind visit

	Total, n	Freedom from failure				Seizure freedom			
		Free from failure, n (%)	OR	95% CI	p Value	Seizure free, n (%)	OR	95% CI	p Value
Obese (BMI for age/sex ≥95th percentile)									
ETX, obese	22	16 (72.7)	2.75	1.01-7.46	0.047 ^a	16 (72.7)	1.63	0.60-4.42	0.342
VPA, obese	18	13 (72.2)	2.68	0.90-7.94	0.075	16 (88.9)	4.89	1.08-22.11	0.040 ^a
LTG, obese	21	4 (19.0)	0.24	0.08-0.76	0.015 ^a	5 (23.8)	0.19	0.07-0.55	0.002 ^a
ETX, not obese	132	65 (49.2)	Reference	—	—	82 (62.1)	Reference	—	—
VPA, not obese	127	72 (56.7)	1.35	0.83-2.20	0.230	87 (68.5)	1.33	0.79-3.33	0.281
LTG, not obese	125	39 (31.2)	0.47	0.28-0.78	0.003 ^a	41 (32.8)	0.30	0.18-0.50	<0.001 ^a
Overweight or obese (BMI for age/sex ≥85th percentile)									
ETX, overweight or obese	56	35 (62.5)	1.88	0.96-3.69	0.064	40 (71.4)	1.72	0.85-3.49	0.130
VPA, overweight or obese	41	24 (58.5)	1.60	0.76-3.34	0.214	28 (68.3)	1.49	0.69-3.21	0.315
LTG, overweight or obese	52	13 (25.0)	0.38	0.18-0.79	0.010 ^a	14 (26.9)	0.25	0.12-0.53	<0.001 ^a
ETX, not overweight or obese	98	46 (46.9)	Reference	—	—	58 (59.2)	Reference	—	—
VPA, not overweight or obese	104	61 (58.7)	1.60	0.92-2.80	0.096	75 (72.1)	1.78	0.99-3.21	0.054
LTG, not overweight or obese	94	30 (31.9)	0.53	0.29-0.95	0.034 ^a	32 (34.0)	0.36	0.20-0.64	0.001 ^a

Abbreviations: BMI = body mass index; CI = confidence interval; ETX = ethosuximide; LTG = lamotrigine; OR = odds ratio; VPA = valproic acid.

^a Significant value.

mutually exclusive and are interdependent. A possible mechanism connecting brain dysfunction to this metabolic web may be related to the neuroendocrine control of energy intake and expenditure, which is influenced by a multitude of neurotransmitters acting on the hypothalamus in response to adiposity signal of leptin and insulin.²⁰ These pathways are incompletely understood and their relationships to behavioral or social influences on the control of net energy excess or deficit are not defined. Our study challenges the role of dietary intake in the obesity-epilepsy

interaction. Surprisingly, the total daily energy consumption and total daily carbohydrate intake were lower in CAE children than in the NHANES group (table 1). Although the difference was only ~80 kcal/day over the total cohort, several factors influence the interpretation of this value. First, because of lack of comparative data about energy expenditure, it is impossible to assess net energy excess or deficit in children with CAE compared to the control cohort. Some evidence suggests that people with epilepsy are relatively less likely to participate

Table 3 Comparison of pharmacokinetic variables (area under the curve exposure and trough levels) in children with body mass index (BMI) ≥85th vs <85th percentile for age/sex for all 3 study drugs

	BMI for age/sex ≥85th percentile		BMI for age/sex <85th percentile		
	N	Median (p ₂₅ -p ₇₅)	N	Median (p ₂₅ -p ₇₅)	p Value
Ethosuximide					
Exposure, µg·h/mL	55	1,044 (737.9-1,505.6)	88	1,123 (710.9-1,657.8)	0.37
Trough levels, µg/mL	55	80.4 (57.6-114.1)	88	87.1 (54.0-127.4)	0.45
Lamotrigine					
Exposure, µg·h/mL	45	99.2 (67.4-134.4)	90	101.2 (61.1-149.2)	0.78
Trough levels, µg/mL	45	6.76 (4.8-9.5)	90	6.8 (3.9-10.0)	0.72
Valproic acid					
Exposure, µg·h/mL	35	1,420.2 (1,124.1-1,626.6)	101	1,485.0 (1,122.5-1,693.5)	0.45
Trough levels, µg/mL	35	101.4 (76.6-121.5)	101	103.5 (76.6-117.9)	0.88

in organized physical activity.²¹ Also, studies have documented a higher proportion of individuals who never exercise among people with epilepsy compared to a control population.^{22,23} Thus, it is possible, although unproven, that children with CAE may be less active than the general population, which may explain the higher BMI despite decreased total energy intake. It will be desirable for future studies to incorporate valid measurements of daily energy expenditure based on activity logs or wearable accelerometer-based devices.²⁴ Second, relatively small differences in daily caloric excess or deficit can cumulatively affect weight changes over longer timeframes. Lastly, the statistical significance of this difference should be interpreted cautiously because there was no correction for multiple comparisons.

Adjustment for maternal education, a surrogate for SES that is another independent predictor of childhood obesity,²⁵ also did not alter the results.

Although no group-level effects of BMI or overweight/obesity status on drug response were identified, this is the first report of pretreatment obesity/overweight being a predictor of differential drug response in newly diagnosed epilepsy. In obese children, efficacy and effectiveness of ETX (FFF OR 2.75) and VPA (SF OR 4.89) were significantly higher and efficacy and effectiveness of LTG were significantly lower (FFF OR 0.24, SF OR 0.19) than in nonobese children on ETX (table 2). This differential efficacy and effectiveness of ETX and VPA over LTG progressively increased with increasing baseline BMI *z* score (figure 2). Few children exited the study because of AED-induced weight gain during the first 16–20 weeks of the trial.⁷

Study drug dosing was weight based.⁸ Although overweight/obese children could have received higher total dose and exposures, analyses found no difference for total exposure or trough levels of children with BMI ≥ 85 th percentile compared to those with <85 th percentile for any of the 3 study AEDs. This suggests that the observed differential efficacy/effectiveness of AEDs in overweight/obese children cannot be attributed to pharmacokinetic factors. There is limited evidence that clearance and volume of distribution vary linearly as a function of body weight and BMI for ETX and VPA in adults.^{26,27} Although this helps inform dosing considerations, there is no evidence that BMI or body weight affects pharmacodynamics. Drug response is determined by multiple pharmacokinetic and pharmacodynamic factors, including dose, target tissue levels, receptor binding, and postreceptor mechanisms. Although our study found no serum pharmacokinetic differences to explain the observed differential efficacy/effectiveness, its design precluded assessment of other tissue-level effects that could have been responsible. Differences in physicochemical

properties of drugs, particularly lipophilicity, which is a determinant of drug concentration in the CNS, could be another potential explanatory variable. Although ETX is the least lipophilic of the study drugs ($\log P = 0.38$, where *P* is octanol-water partition coefficient), the $\log P$ values for LTG (1.87) and VPA (2.75) are not considerably different.²⁸ Similar unexplained differential effect of baseline BMI/obesity status has been reported for other neuroactive medications.²⁹ At present, the interaction between baseline BMI or overweight/obesity status, weight-related effects of AEDs themselves, and differential drug response remains to be fully characterized.

Children with newly diagnosed CAE had increased prevalence of overweight and obesity compared to normative US peers despite a lower mean daily energy and carbohydrate intake. Furthermore, overweight/obesity status or increasing BMI *z* score was associated with improved seizure outcomes in those receiving ETX and VPA and worse outcomes in patients on LTG compared to weight-appropriate children with CAE. This differential treatment response could not be explained by pharmacokinetics because there were no significant differences in drug exposure and trough levels between overweight/obese children and those with appropriate body weight. These results do not alter the original randomized controlled trial's conclusion that ETX is the preferred initial therapy for CAE.⁷ It is hoped that physiologic mechanisms underlying these findings will be elucidated in the future and, together with other analyses emerging from the CAE study, a multivariable predictive model of patient-specific factors influencing drug selection will be possible.

AUTHOR CONTRIBUTIONS

Study concept and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content: R.A., C.W.G., P.C., S.S., A.C., T.A.G. Study supervision: T.A.G. Statistical analysis: C.W.G., A.C., R.A. wrote the first draft of the manuscript. All authors approved the final version. All authors had full access to all the data in the study. T.A.G. and A.C. take responsibility for the integrity of the data and the accuracy of the data analysis.

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