Second monotherapy in childhood absence epilepsy

Avital Cnaan, PhD
Shlomo Shinnar, MD, PhD
Ravindra Arya, MD, DM
Peter C. Adamson, MD
Peggy O. Clark, DNP, PPCNP-BC
Dennis Dlugos, MD
Deborah G. Hirtz, MD
David Masur, PhD
Tracy A. Glauser, MD
For the Childhood Absence Epilepsy Study Group

Correspondence to Dr. Cnaan: acnaan@trinds.com

ABSTRACT

Objective: To determine optimal second monotherapy for children with childhood absence epilepsy (CAE) experiencing initial treatment failure.

Methods: Children with CAE experiencing treatment failure during the double-blind phase of a randomized controlled trial comparing ethosuximide, valproic acid, and lamotrigine were randomized to open-label second monotherapy with one of the 2 other study therapies. Primary study outcome was freedom from failure proportion at week 16–20 and month 12 visits after randomization. Secondary study outcome was percentage of participants experiencing attentional dysfunction at these visits.

Results: A total of 208 children were enrolled, randomized, and received second therapy. At both week 16–20 visit and month 12 visit, ethosuximide's (63%, 57%) and valproic acid's (65%, 49%) freedom from failure proportions were similar to each other and higher than lamotrigine's (45%, 36%, $p = 0.051$ and $p = 0.062$). At both time points, ethosuximide and valproic acid had superior seizure control compared to lamotrigine ($p < 0.0001$). At both the week 16–20 and month 12 visits, attentional dysfunction was numerically more common with valproic acid than with ethosuximide or lamotrigine. For each medication, second monotherapy freedom from failure proportions demonstrated noninferiority to initial monotherapy freedom from failure proportions.

Conclusions: As second monotherapy, ethosuximide and valproic acid, demonstrated higher freedom from failure proportions and greater efficacy than lamotrigine; valproic acid was associated with more attentional dysfunction. Ethosuximide is the optimal second monotherapy for children with CAE not responding to initial therapy with other medications.

ClinicalTrials.gov identifier: NCT00088452.

Classification of evidence: This study provides Class III evidence that for children with CAE experiencing initial treatment failure, second monotherapy with ethosuximide or valproic acid is superior to lamotrigine. *Neurology*® 2017;88:182–190

GLOSSARY

AED = antiepileptic drug; **CAE** = childhood absence epilepsy; **CI** = confidence interval; **CPT** = Continuous Performance Test; **FFF** = freedom from treatment failure; **GTC** = generalized tonic-clonic; **ILAE** = International League Against Epilepsy; **OR** = odds ratio; **RCT** = randomized clinical trial.

A double-blind randomized clinical trial (RCT) compared ethosuximide, lamotrigine, and valproate as initial monotherapy for children with newly diagnosed childhood absence epilepsy (CAE).[1,2] Freedom from treatment failure (FFF) was assessed at week 16–20 and at month 12 of therapy. The FFF rates at these 2 timepoints for ethosuximide were 53% and 45%, valproate 58% and 44%, and lamotrigine 29% and 21%.[1,2] Ethosuximide was identified as the optimal initial therapy due to superior efficacy compared with lamotrigine and similar efficacy but fewer attentional side effects when compared to valproate. However, initial monotherapy failed in a substantial proportion of children with CAE.[1,2]

Supplemental data at Neurology.org

From Children's National Health System (A.C.), Washington, DC; Montefiore Medical Center (S.S., D.M.), Albert Einstein College of Medicine, New York, NY; Cincinnati Children's Hospital Medical Center and the University of Cincinnati College of Medicine (R.A., P.O.C., T.A.G.), OH; The Children's Hospital of Philadelphia and Perelman School of Medicine at the University of Pennsylvania (P.C.A., D.D.); and National Institute of Neurological Disorders and Stroke (D.G.H.), Bethesda, MD.

Childhood Absence Epilepsy Study Group coinvestigators are listed at Neurology.org.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

© 2016 American Academy of Neurology

© 2016 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

Failure of initial therapy is not limited to children with CAE. Approximately 50% of adults and children with epilepsy achieve success with their first antiepileptic drug (AED).[3–8] There are limited data from cohort studies about response to second therapy in children with other seizure types[9,10] and long-term remission rates for children with CAE experiencing initial drug failure,[11,12] but there are no rigorous clinical trial data about the optimal second monotherapy for children with CAE.

This CAE clinical trial provided a unique opportunity to examine clinical response to second monotherapy in a well-characterized cohort whose initial monotherapy failed. We report outcomes for participants whose initial double-blind treatment failed and who subsequently enrolled in an open-label randomized comparative study of second monotherapy using the same study AEDs.

METHODS

Primary research question. What is the optimal second monotherapy for children with CAE whose initial monotherapy failed for any reason?

Participant population. Children were eligible if they had participated in the CAE trial,[1,2] experienced initial monotherapy failure, and, at the time of second monotherapy enrollment, met the same eligibility criteria as in the original study with 2 exceptions. Participants who experienced a generalized tonic-clonic (GTC) seizure on initial monotherapy were eligible. Girls could be postmenarchal at second monotherapy enrollment if they agreed to abstain from sexual intercourse. Children were ineligible if they had developed a clinically significant systemic disease, major psychiatric or developmental disorder, or if they were considered to be nonadherent by the site study team.

Study design. Participants experiencing treatment failure on blinded initial monotherapy were tapered during a blinded conversion period with option to use a benzodiazepine bridge. Open-label second monotherapy was started at least 2 weeks after the last dose of initial monotherapy and after the benzodiazepine bridge was stopped.

Eligible participants were randomly assigned (1:1) to receive 1 of the 2 AEDs not given as initial monotherapy, with specific exceptions. Participants exiting initial monotherapy due to a GTC seizure were not randomized to ethosuximide, participants exiting due to a rash or on systemic contraceptives for any reason were not randomized to lamotrigine, and participants exiting due to hepatitis or pancreatitis were not randomized to valproate. These participants were assigned to the appropriate remaining medication rather than randomized. Treatment assignment was performed centrally using permuted blocks of 4 within <6 years and ≥ 6 years age strata.

Open-label second monotherapy study visits occurred every 4 weeks for the first 16 weeks, at 26 weeks, and then every 6 months. Medication was titrated as tolerated in predetermined increments[1,2] every 1–2 weeks until the week 16 visit. Titration continued only until the participant achieved either seizure freedom by clinical and EEG criteria or reached the maximal allowed or maximal tolerated dose. Maximal allowed doses were (the lower of) ethosuximide 60 mg/kg/d or 2,000 mg/d; lamotrigine 12 mg/kg/d or 600 mg/d; valproate 60 mg/kg/d or 3,000 mg/d. If parents reported ongoing absence seizures or seizures were captured either on bedside hyperventilation or a 1-hour EEG, then an upward titration was done. If no seizures were reported or noted at both bedside hyperventilation and 1-hour EEG, then medication dosage was not changed. An electrographic seizure was defined as ≥ 3 seconds of generalized spike-and-wave discharge on EEG. At every study visit, complete blood counts and liver panels were assessed.

At the week 16 visit, participants who were both clinically and electrographically seizure-free were considered seizure-free. Participants at their maximal allowed or maximal tolerated dose with clinical/electrographic seizures were considered to have met a treatment failure criterion. Participants not yet at maximal allowed dose with clinical/electrographic seizures were allowed a single additional dose escalation and repeat EEG 4 weeks later (week 20). Participants with clinical/electrographic seizures at the week 20 visit were considered treatment failures.

This study's methodology was identical to that of the initial RCT.[1,2] If there was FFF at the week 16–20 visit, participants continued second monotherapy until 24 months of seizure freedom. If a treatment failure criterion was reached earlier, participation in the clinical trial ended.

Study medications (ethosuximide, valproate, and lamotrigine) were provided by Pfizer Inc. (New York, NY), Abbott Laboratories (Abbott Park, IL), and GlaxoSmithKline (Brentford, UK), respectively. The study central pharmacy shipped the medications to the local site pharmacy, where it was dispensed to the participants.

Study outcomes. The study's primary outcome was FFF. Treatment failure was defined as ongoing absence seizures at or after the week 16–20 visit, a GTC or other nonabsence seizure at any time, platelet count $<50{,}000/mm^3$, absolute neutrophil count $<500/mm^3$, alanine aminotransferase or aspartate aminotransferase level ≥ 10 times upper limit of normal, total bilirubin level ≥ 5 times upper limit of normal, a moderately severe (possibly drug-related) rash, pancreatitis, increase in body mass index of ≥ 3.0 units from second monotherapy initiation, patient/family identified intolerable side effects after a single downward dose modification, or patient/family/physician desire to withdraw from study. Failure was determined using identical methodology to the initial monotherapy trial.[1,2] Ongoing absence seizures included parental report of multiple absence seizures or ≥ 1 seizures captured on study EEG. Secondary outcome was the Confidence Index on the Conners Continuous Performance Test (CPT).[1,2,13] A value of ≥ 0.60 was considered evidence of clinically significant attention difficulties.[1,2,13,14]

Statistical methods. Baseline and safety characteristics were compared between treatments using either an exact χ^2 test or a 2-way analysis of variance, with treatment and age strata as factors. Outcome analyses used a modified intention-to-treat approach with all randomized participants who received at least one dose of second monotherapy included in the analyses.

At week 16–20 and month 12 visits, primary and secondary outcomes were compared separately using Fisher exact tests on pairwise comparisons between treatments, using a p value of 0.017 (Bonferroni correction). An overall exact χ^2 test, an odds ratio (OR) calculation with a 95% confidence interval (CI), and a logistic regression adjusting for any covariates that were not balanced between treatments at second monotherapy baseline were performed.

In order to test whether survival curves were similar or different, Fleming-Harrington (p, q) tests were done using weights determined by powers p and q.[15] P and q equal to 0 gave the

© 2016 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

log-rank test results, and p = 0, q = 1 focused on later separation between curves by AED.[16]

Initial monotherapy FFF was compared to second monotherapy FFF using a noninferiority analysis. A therapy was considered noninferior as second monotherapy if the second monotherapy FFF rate was no worse than 10% lower than the same therapy's initial monotherapy FFF rate. Within each second monotherapy treatment group, the FFF proportions were also compared between the 2 initial monotherapy groups using a Fisher exact test.

The same decision-making algorithm used to determine optimal initial monotherapy in the initial monotherapy trial[1,2] was used for this trial. Optimal therapy was determined first by comparing FFF rates and then using CPT confidence index as a tie-breaker between equally efficacious AEDs if needed. Primary analyses were prespecified. Analyses comparing participants and those not participating and whether the outcome of second monotherapy depended on first monotherapy were additional. All analyses were performed using SAS (Cary, NC) software version 9.1.

Standard protocol approvals, registrations, and patient consents. The institutional review boards of each site, the coordinating center, and the NIH appointed data and safety monitoring board approved the study. Parents/guardians provided written informed consent and, when applicable, assent was obtained. The RCT was conducted under a Food and Drug Administration–approved Investigational New Drug application. The study is listed at clinicaltrials.gov/ under identifier NCT00088452.

RESULTS **Participant characteristics.** Among the 446 children enrolled in the initial monotherapy RCT, 129 had long-term FFF and 103 declined participation in the second monotherapy trial. Thus, 214 children were enrolled and randomized to second monotherapy. Following randomization, 4 participants never received drug and 2 participants were ineligible due to low absolute neutrophil counts. The remaining 208 participants formed the second monotherapy cohort (figure e-1 at Neurology.org).

There were no differences in baseline age, body mass index, sex, ethnicity, or baseline initial monotherapy CPT scores between the 208 children in the second monotherapy cohort and the participant group whose initial monotherapy was successful (n = 129), the group whose initial monotherapy failed but were not part of this second monotherapy study (n = 109), or these groups combined (n = 238). There was a higher proportion of black participants in the group that was not part of the second monotherapy cohort (35/109, 32% vs 27/208, 13%, $p < 0.001$). In addition, the initial monotherapy success group (n = 129) had higher baseline IQ than the second monotherapy cohort (n = 208) and the initial monotherapy failure cohort who were not part of this study (n = 109) (table e-1). Within this study's second monotherapy group, there were no differences in baseline (pretreatment) variables among the 3 treatment arms (table e-2).

FFF outcome. At the week 16–20 visit, 123 (59%) of the 208 children met FFF criteria (table 1). FFF proportions were ethosuximide 63%, valproate 65%, and lamotrigine 45% ($p = 0.051$). Pairwise comparisons showed higher FFF proportions for ethosuximide compared to lamotrigine (OR 2.01, 95% CI 0.99–4.09) and valproate compared to lamotrigine (OR 2.27, 95% CI 1.12–4.59). The main reasons for treatment failure (multiple reasons allowed per participant) were lack of seizure control (n = 49/208, 23.6%), intolerable side effects (n = 29/208, 13.9%), and participant withdrawal (n = 20/208, 9.6%). Compared to both ethosuximide and valproate, lamotrigine has significantly higher proportions of uncontrolled seizures and lower proportions of intolerable adverse events.

At the month 12 visit, 101 (49%) of the 208 children still met FFF (table 2). FFF proportions were ethosuximide 57%, valproate 49%, and lamotrigine 36% ($p = 0.062$). Pairwise comparisons showed higher FFF proportions for ethosuximide compared to lamotrigine (OR 2.35, 95% CI 1.15–4.81) but no difference for valproate compared to the other treatments. At the month 12 visit, lamotrigine continued to have significantly higher proportions of uncontrolled seizures and lower proportions of intolerable adverse events compared to both ethosuximide and valproate. Adding race as a covariate in logistic regressions did not alter the results.

Time to failure curves for second monotherapy are shown in figure 1. The curves show a lack of proportional hazards between the AEDs over time, making the log-rank test less useful to compare the curves. While the log-rank test did not detect a difference among the 3 medications, the Fleming-Harrington test with p = 0, q = 1 demonstrated a significant difference between curves ($p = 0.002$) along with a difference for lamotrigine compared to ethosuximide + valproate ($p = 0.003$).

At both timepoints, for each medication, second monotherapy failure rates were no higher than initial monotherapy failure rates (table 3). The risk differences and 95% CIs were within the prespecified 10% threshold for each AED. Noninferiority between second monotherapy and first monotherapy was also evident for the multiple treatment failure subcategories. The week 16–20 and month 12 FFF proportions for each of the second open-label monotherapy arms were not differentially affected by the specific initial double-blind monotherapy used (table e-3).

Attention outcomes. CPT data were available for 81% (169/208) of participants at the week 16–20 visit and 87% of participants (107/123) reaching the month 12 visit. At both timepoints, the percentage of second monotherapy valproate participants with a confidence index ≥0.60 were numerically higher compared to that for both ethosuximide and lamotrigine second

© 2016 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

Table 1 Primary outcome and reasons for treatment failure at weeks 16–20 of second monotherapy

Result	ETX (n = 75), n (%)	LTG (n = 55), n (%)	VPA (n = 78), n (%)	Overall *p* value	ETX vs LTG		VPA vs ETX		VPA vs LTG	
					p Value[a]	OR (95% CI)	*p* Value[a]	OR (95% CI)	*p* Value[a]	OR (95% CI)
Freedom from treatment failure	47 (63)	25 (45)	51 (65)	0.051	0.074	2.01 (0.99–4.09)	0.74	1.13 (0.58–2.18)	0.032	2.27 (1.12–4.59)
Treatment failures	28 (37)	30 (55)	27 (35)							
Lack of seizure control	11 (15)	26 (47)	12 (15)	<0.0001	<0.0001	0.19 (0.08–0.44)	1.0	1.06 (0.44–2.57)	<0.0001	0.20 (0.09–0.46)
EEG seizures only	7	17	7							
Seizures either on clinical report or on bedside hyperventilation only	3	2	1							
Seizures on EEG and on clinical report or seizures on EEG and on bedside hyperventilation	1	7	2							
Other type of seizures (GTC, focal)	0	0	2							
Intolerable AEs	13 (17)	2 (4)	14 (18)	0.036	0.024	5.56 (1.20–25.74)	1.0	1.04 (0.45–2.40)	0.014	5.80 (1.26–26.65)
Nervous system, behavioral, or psychological effects	5	1	4							
Digestive disorders	5	1	2							
Rash	1	1	0							
Unacceptable weight gain	0	0	6							
Pancreatitis	0	0	2							
Fatigue	1	0	0							
Other[b]	3	0	3							
Study/patient-related withdraw	9 (12)	4 (7)	7 (9)	0.67	0.56	1.74 (0.51–5.97)	0.60	0.72 (0.25–2.05)	1.0	1.26 (0.35–4.52)
Local investigator's decision	1	1	1							
Parent or guardian's decision	6	2	6							
Local investigator's and parent or guardian's decision	2	1	0							

Abbreviations: CI = confidence interval; ETX = ethosuximide; GTC = generalized tonic-clonic; LTG = lamotrigine; OR = odds ratio; VPA = valproate.
[a] *p* Values were calculated from exact χ^2 test for the overall test and Fisher exact test for the pairwise comparisons.
[b] Other intolerable adverse effects (AEs) that led to treatment failures are nonspecified parent-reported intolerant AEs.

© 2016 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

© 2016 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

Table 2 Outcomes and reasons for treatment failure at month 12 of second monotherapy for each treatment arm

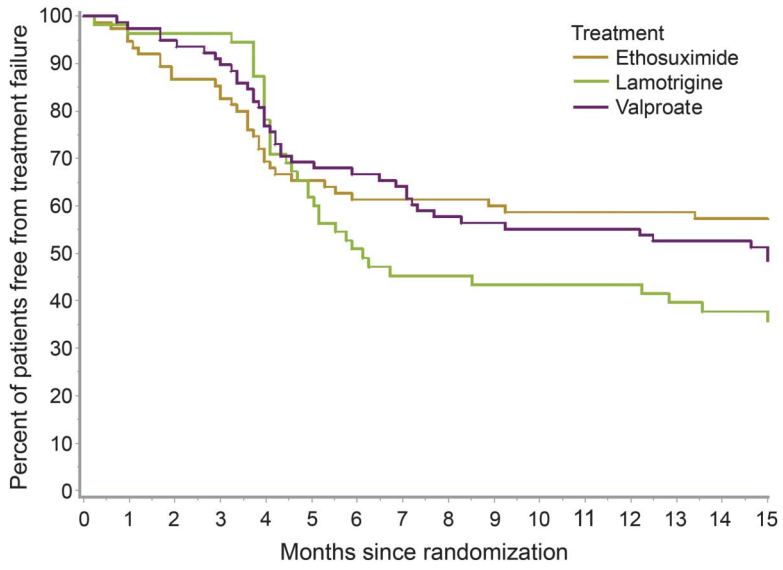
Results	ETX (n = 75), n (%)	LTG (n = 55), n (%)	VPA (n = 78), n (%)	Overall *p* value	ETX vs LTG		VPA vs ETX		VPA vs LTG	
					p Value[a]	OR (95% CI)	*p* Value[a]	OR (95% CI)	*p* Value[a]	OR (95% CI)
Freedom from treatment failure	43 (57)	20 (36)	38 (49)	0.062	0.022	2.35 (1.15–4.81)	0.33	0.71 (0.37–1.34)	0.21	1.66 (0.82–3.37)
Treatment failures	32 (43)	35 (64)	40 (51)							
Lack of seizure control	13 (17)	30 (55)	15 (19)	<0.0001	<0.0001	0.17 (0.08–0.39)	0.84	1.14 (0.50–2.58)	<0.0001	0.20 (0.09–0.43)
EEG seizures only	8	21	8							
Seizures either on clinical report or bedside hyperventilation only	4	2	2							
Seizures on EEG and on clinical report or seizures on EEG and on bedside hyperventilation	1	7	2							
Generalized tonic-clonic seizures	0	0	2							
Focal seizures	0	0	1							
Intolerable adverse effects	14 (19)	3 (5)	21 (27)	0.0065	0.035	3.98 (1.08–14.61)	0.25	1.61 (0.75–3.46)	0.0013	6.39 (1.80–22.67)
Nervous system, behavioral, or psychological effects	5	1	6							
Digestive disorders	5	1	2							
Rash	1	1	0							
Unacceptable weight gain	0	1	8							
Pancreatitis	0	0	2							
Fatigue	1	0	2							
Hair loss	0	0	1							
Other[b]	4	0	5							
Study/patient-related withdraw	10 (13)	5 (9)	12 (15)	0.55	0.58	1.54 (0.49–4.79)	0.82	1.18 (0.48–2.93)	0.43	1.82 (0.60–5.50)
Local investigator's decision	1	1	1							
Parent or guardian's decision	7	3	10							
Local investigator's and parent or guardian's decision	2	1	1							

Abbreviations: CI = confidence interval; ETX = ethosuximide; GTC = generalized tonic-clonic; LTG = lamotrigine; OR = odds ratio; VPA = valproate.

[a] *p* Values were calculated from exact χ^2 test for the overall test and Fisher exact test for the pairwise comparisons.

[b] Other intolerable adverse effects (AEs) that led to treatment failures include laboratory (low platelet counts), lupus, and nonspecified parent-reported intolerant AEs.

Figure 1 Survival curve of second therapy treatment by 1 year



Log-rank test for 3 treatments, $p = 0.21$; Fleming-Harrington with $p = 0$, $q = 1$ for 3 treatments, $p = 0.002$; for lamotrigine vs ethosuximide + valproate, $p = 0.003$.

monotherapy participants. The pairwise comparison between valproate and ethosuximide at the week 16–20 visit demonstrated a substantial effect on attention (44% vs 28%, $p = 0.09$) (table 4).

Adverse events. During the first 12 months, 5 participants (2%) experienced serious adverse events requiring hospitalization (4 valproate, 1 lamotrigine), including 3 cases of pancreatitis (valproate), a case of gastroenteritis, esophagitis, and dehydration (lamotrigine), and 1 case of a single cluster of focal seizures (valproate). All events resolved. There were 2 cases of rash leading to treatment failure (1 lamotrigine, 1 ethosuximide) but no cases of Stevens-Johnson syndrome. There were 2 participants on valproate who developed GTC seizures.

Over the first 12 months, 23 types of adverse events (4 different body systems) were spontaneously reported by ≥5% of participants in at least one AED (table e-4). Most adverse events occurred early in therapy, were transient, and were mild to moderate in severity. At least one adverse event was reported by 89% (187/208) of participants but only 14% (29/208) discontinued due to intolerable adverse events.

DISCUSSION This second monotherapy RCT showed clear differences between medications in effectiveness, efficacy, tolerability, and effects on attention. Ethosuximide and valproate demonstrated superior effectiveness compared to lamotrigine with FFF rates similar to those seen in the larger initial monotherapy RCT. At both 16–20 weeks and 12 months, there was a >20% relative difference for both ethosuximide (63% vs 45%) and valproate (65% vs 45%) compared to lamotrigine. These effectiveness differences meet the threshold for clinical significance established by the 1998 International League Against Epilepsy (ILAE) Commission on Antiepileptic Drugs.[17,18]

In exploring the Kaplan-Meier curves of time to treatment failure, the log-rank test did not achieve significance. However, the log-rank test is only optimal to detect differences in time to event under the proportional hazards model assumption.[19] If there are early or late effects and the curves cross from one pattern to a different pattern later, or the curves separate (both apparent in figure 1), the proportional hazards assumption is not met, and the Fleming-Harrington approach with $p = 0$, $q > 0$ performs better to identify the early or late effects.[16,20] It is often difficult to know a priori in a clinical trial whether the proportional hazards assumption, implying the choice of the log-rank test, will be appropriate. The choice of performing the Fleming-Harrington test in this study was based on figure 1.

Children on valproate had a higher proportion of participants with abnormal CPT confidence index scores. The p value of 0.09 does not invalidate the medication effect interpretation[21]; while the numbers were smaller than the original RCT, the effect size was similar.[2,13]

The proportions of tolerable side effects were comparable and sometimes lower in the open-label second therapy than in the initial RCT. Most tolerable side effects occur early in therapy; the proportion of new occurrences after the first 16–20 weeks is fairly low except weight gain. The number of GTC seizures on initial valproate ($n = 6$) and lamotrigine ($n = 1$) monotherapy was very low[22] and therefore unlikely to introduce bias.

Few studies have examined response to second therapy. The best known study involved a cohort from Glasgow, where 1,098 people with epilepsy, mainly adults with focal epilepsy, were followed for a median of 7.5 years. One-year terminal remission rate for initial monotherapy was 49.5%. A total of 398 patients were treated with a second monotherapy and had a 1-year terminal remission rate of 26.3% among the initial treatment failures (13.3% rate for the overall cohort).[3,8,13,23] This series of publications established the concept that failure to respond to initial therapy was an unfavorable prognostic sign for response to second or later therapies.

Four pediatric studies have examined response to second therapy in a mixed population of children with epilepsy. The Dutch study of epilepsy in childhood followed 453 children for 5 years. The first monotherapy 1-year terminal remission rate was 46.0% while the second monotherapy 1-year terminal remission rate was 35.2% among the initial treatment failures (19.0% rate for the overall cohort).[5] In a 2009 report, 343 children were followed for 2 years. The first monotherapy 1-year terminal remission rate was

© 2016 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

Table 3 Noninferiority test of second monotherapy compared to initial monotherapy on all outcomes within treatment groups

		Week 16-20 visit						Month 12 visit					
		Initial monotherapy		Second monotherapy				Initial monotherapy		Second monotherapy			
Outcome	AED	n	Failure proportion	n	Failure proportion	Risk difference (95% CI)	p Value	n	Failure proportion	n	Failure proportion	Risk difference (95% CI)	p Value
Failure due to any reason	ETX	73	0.47	28	0.37	0.10 (−0.034-0.24)	0.0018	84	0.55	32	0.43	0.12 (−0.018-0.26)	0.0009
	LTG	103	0.71	30	0.55	0.16 (0.0091-0.31)	0.0004	115	0.79	35	0.64	0.15 (0.0079-0.29)	0.0003
	VPA	61	0.42	27	0.35	0.072 (−0.061-0.20)	0.0055	82	0.56	40	0.51	0.049 (−0.088-0.19)	0.017
Failure due to seizure	ETX	23	0.15	11	0.15	0.003 (−0.095-0.10)	0.020	25	0.16	13	0.17	−0.011 (−0.12-0.093)	0.046
	LTG	73	0.50	26	0.47	0.027 (−0.13-0.18)	0.054	81	0.55	30	0.55	0.0093 (−0.15-0.16)	0.083
	VPA	20	0.14	12	0.15	−0.017 (−0.11-0.081)	0.048	22	0.15	15	0.19	−0.042 (−0.15-0.063)	0.14
Failure due to AEs	ETX	37	0.24	13	0.17	0.067 (−0.042-0.18)	0.0013	38	0.25	14	0.19	0.060 (−0.051-0.17)	0.0024
	LTG	25	0.17	2	0.036	0.13 (0.056-0.21)	<0.0001	29	0.20	3	0.055	0.14 (0.056-0.23)	<0.0001
	VPA	35	0.24	14	0.18	0.060 (−0.050-0.17)	0.0021	48	0.33	21	0.27	0.060 (−0.065-0.18)	0.006
Failure due to withdraw	ETX	19	0.12	9	0.12	0.003 (−0.087-0.093)	0.012	29	0.19	10	0.13	0.055 (−0.044-0.15)	0.001
	LTG	18	0.12	4	0.07	0.051 (−0.036-0.14)	0.0003	18	0.12	5	0.091	0.032 (−0.060-0.13)	0.0026
	VPA	15	0.10	7	0.090	0.013 (−0.067-0.093)	0.0029	21	0.14	12	0.15	−0.010 (−0.11-0.088)	0.036

Abbreviations: AE = adverse effect; AED = antiepileptic drug; CI = confidence interval; ETX = ethosuximide; LTG = lamotrigine; VPA = valproate.
For ETX: initial monotherapy n = 154, second monotherapy n = 75; for LTG: initial monotherapy n = 146, second monotherapy n = 55; for VPA: initial monotherapy n = 146, second monotherapy n = 78. For each analysis, the hypothesis being tested is whether the failure proportion on second monotherapy is worse than 10% higher than on the initial monotherapy. As the numeric percentages show, in all cases either the failure proportion was lower on second monotherapy than on initial monotherapy or it was only 1% higher, showing clearly that second monotherapy was not inferior, and, at least numerically, in many cases, superior.

60.8% while the second monotherapy 1-year terminal remission rate was 30.6% among initial treatment failures (8.4% overall rate).[24] In the Nova Scotia cohort (n = 417), 42% (30/72) of children with inadequate seizure control on their first AED achieved complete remission of their seizures with second monotherapy.[10] Key methodologic differences compared with the current study were an unclear timeframe for seizure remission, inclusion of children with GTC and partial seizures, exclusion of children with absence seizures, efficacy (seizure control) instead of effectiveness outcome, and variable treatment protocols. Another small study (n = 24) including children with partial-onset seizures found second monotherapy to achieve seizure control in 29% (7/24).[9]

In contrast, this study demonstrates that, 12 months after medication initiation, children with CAE can respond as well with second monotherapy (49%, 101/208) as with initial monotherapy (37%, 165/446). This response to second therapy is not affected by choice of initial monotherapy. The median ages of the initial and second monotherapy cohorts were 7.4 and 7.7 years. There is no evidence that such a small age difference could significantly affect spontaneous remission. Despite this reassuring and surprising finding, the overall response to initial

Table 4 Elevated confidence index scores (≥0.60) at baseline visit, 16-20 weeks visit, and month 12 visit per treatment group

Visit	Ethosuximide, % (n)	Lamotrigine, % (n)	Valproate, % (n)	Overall p value at that visit	Ethosuximide vs valproate: p value
Baseline	32 (21/66)	34 (17/50)	38 (27/71)	0.75	0.48
Week 16-20 visit	28 (16/58)	34 (16/47)	44 (28/64)	0.18	0.09
Month 12 visit	34 (14/41)	30 (7/23)	49 (21/43)	0.23	0.19

The initial monotherapy study's baseline Continuous Performance Test (CPT) results were used as this study's baseline CPT measures.

© 2016 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

and second therapy is still not ideal and leaves approximately one-third of CAE patients with ongoing seizures, meeting the ILAE criteria for drug-resistant.[25]

An ongoing follow-up study of this cohort is examining whether outcomes 6 years postdiagnosis are affected by initial choice of therapy, response to initial monotherapy, or response to second monotherapy. For children with CAE, the ultimate impact of precision medicine (the right drug for the right patient at the right time) will be closely linked to this answer.

As second therapy for children with CAE, ethosuximide and valproate demonstrated higher FFF rates than lamotrigine. Response rate to second monotherapy was similar to that seen for initial monotherapy. Valproate is associated with more attentional dysfunction than the other study medications. Failure of initial therapy did not affect response to second therapy. Overall, ethosuximide is the optimal second monotherapy for children with CAE not responding to initial monotherapy.

AUTHOR CONTRIBUTIONS

Study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, study supervision: A. Cnaan, S. Shinnar, R. Arya, P.C. Adamson, P. Clark, D. Dlugos, D.G. Hirtz, D. Masur, T.A. Glauser. Statistical analysis: A. Cnaan. Drs. Cnaan and Glauser wrote the first draft of the manuscript. Drs. Cnaan, Shinnar, Adamson, Dlugos, Hirtz, Masur, Clark, and Glauser had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

ACKNOWLEDGMENT

Contributors: Peter C. Adamson, MD (The Children's Hospital of Philadelphia, Executive Committee); Brian K. Alldredge, PharmD (University of California San Francisco, Data and Safety Monitoring Board); Tina Alvarado-Taylor (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, Randomization Specialist); Anne Berg, PhD (Children's Memorial Hospital, Chicago, EEG/Clinical Phenotyping Core); Gordon Bernhard (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, Data Entry); Blaise Bourgeois, FD, MD (Boston Children's Hospital, Data and Safety Monitoring Board); Brooke Bintliff-Janisak (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, CRA); Jeffrey Blumer, MD, PhD (University Hospitals Rainbow Babies and Children's Hospital, Cleveland, Executive Committee, Pharmacokinetics Core); Jeffrey R. Buchhalter, MD, PhD (Phoenix Children's Hospital, Data and Safety Monitoring Board); Edmund V. Capparelli, PharmD (University of California, San Diego, Executive Committee, Pharmacokinetics Core); Joan A. Conry, MD (Children's National Health System, EEG/Clinical Phenotyping Core); Jeanine Dahlquist, MS (Cincinnati Children's Hospital, Childhood Absence Epilepsy Coordinating Center, Data Quality Specialist); Kaitlyn Daniels (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, CRA); Mignon Davis (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, Database Designer); Julie DiStefano-Pappas (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, Data Manager); Michael Donaghue (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, Systems Administrator); Eileen Dorsey (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, Operations Manager); Nakeshia Drummond (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, Data Entry); Shonda Evans (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, CRA); Brandy E. Fureman, PhD (National Institute of Neurological Disorders and Stroke, Program Official); Peter R. Gilbert, ScM (National Institute of Neurological Disorders and Stroke, Data and Safety Monitoring Board); Melanie Gleave (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, CRA); Gregory A. Grabowski, MD (Cincinnati Children's Hospital, Pharmacogenetic Core); Rong Guo, MS (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, Biostatistician); Melissa Grubb (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, Data Entry); Marla J. Hamberger, PhD (The Neurological Institute of New York at Columbia University, Data and Safety Monitoring Board); Dale Hesdorffer, PhD (Columbia University, Sergievsky Center, Neuropyschology/QOL); Emily Hirschfeld (Cincinnati Children's Hospital, Childhood Absence Epilepsy Coordinating Center, Operations Manager); Michael Hoffman, RPh (Cincinnati Children's Hospital, Research Pharmacy Central Pharmacist); Fengming Hu, MS (Children's National Health System, Childhood Absence Epilepsy Coordinating Center, Biostatistician); Paula Jackson (Cincinnati Children's Hospital, Childhood Absence Epilepsy Coordinating Center, CRA); Margaret Jacobs (National Institute of Neurological Disorders and Stroke, NINDS Program Official); Mehdi Keddache, PhD (Cincinnati Children's Hospital, Pharmacogenetics Core); Sudha K. Kessler, MD (The Children's Hospital of Philadelphia, EEG/Clinical Phenotyping Core); Michael Kuhlmann (Cincinnati Children's Hospital, Childhood Absence Epilepsy Coordinating Center, Research Database Programmer); Denise LaGory, RPh (Cincinnati Children's Hospital, Research Pharmacy Central Pharmacist); Laura Lawrence (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, Randomization Specialist); Paul M. Levisohn, MD (The Children's Hospital, Denver, Neuropsychology/QOL Core); David Loring, PhD (Emory University, Neuropsychology/QOL Core); Xianqun Luan, MS (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, Biostatistician); Chunyan Liu, MS (Cincinnati Children's Hospital, Childhood Absence Epilepsy Coordinating Center, Biostatistician); Jonathan Masur (Montefiore Medical Center and the Albert Einstein College of Medicine, Bronx, NY, Neuropsychology/QOL Core, Central Psychometrist); Susan McMahan, RN (Cincinnati Children's Hospital Childhood Absence Epilepsy Coordinating Center, Recruitment Specialist); Katherine Montefiore, RPh (Cincinnati Children's Hospital, Research Pharmacy); Guriya Nandwani, MD (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, Operations Manager); John Nevy (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, Data Coordination); Virginia Nissen, MS (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, Operations Manager); Valerie O'Brien (Cincinnati Children's Hospital, Pharmacogenetics Core); Philip Overby, MD (Montefiore Medical Center and the Albert Einstein College of Medicine, Bronx, NY, EEG/Clinical Phenotyping Core); Nicholas Peccina (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, Systems Administrator); John M. Pellock, MD (Medical College of Virginia, Virginia Commonwealth University, Medical Safety Monitor); John P. Pestian, PhD (Cincinnati Children's Hospital, Childhood Absence Epilepsy Coordinating Center, Data Management Core); Michael D. Reed, PharmD, FCCP, FCP (Case Western Reserve University School of Medicine, Pharmacokinetics Core); John H. Rodman, PharmD (deceased) (St. Jude Children's Research Hospital, Memphis, Data and Safety Monitoring Board); Ellen B. Roecker, PhD (Department of Biostatistics and Medical Informatics, University of Wisconsin, Madison, Data and Safety Monitoring Board); Julie Schneider (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, CRA); Charles Scott, PhD (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, Biostatistician); Mayadah Shabbout, MA (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, Biostatistician); David Shera ScD (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, Biostatistician); Ruth C. Shinnar, RN, MSN (Albert Einstein College of Medicine, Montefiore Medical Center, Neuropsychology/QOL Core); Sarah Srodulski (Cincinnati Children's Hospital, Pharmacogenetics Core); Gerri Tangren (Cincinnati Children's Hospital, Pharmacogenetics Core); Marc Taylor (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, Data Entry); Nirmala Thevathasan (The Children's Hospital of Philadelphia, Childhood Absence

© 2016 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

Epilepsy Coordinating Center, Operations Manager); Tonia Toon (Cincinnati Children's Hospital, Childhood Absence Epilepsy Coordinating Center, Operations Manager); Maria Vasconcelos (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, CRA); Alexander A. Vinks, PharmD, PhD, FCP (Cincinnati Children's Hospital, Pharmacokinetics Core); Gretchen Von Allmen, MD (Baylor College of Medicine, Houston, EEG/Clinical Phenotyping Core); Clare Weiler (The Children's Hospital of Philadelphia, Childhood Absence Epilepsy Coordinating Center, Operations Manager); Erica F. Weiss, MA (Montefiore Medical Center and the Albert Einstein College of Medicine, Bronx, NY, Neuropsychology/QOL Core and Central Psychometrist); Sheila Wolfer (Cincinnati Children's Hospital, Childhood Absence Epilepsy Coordinating Center, Data Coordinator).

STUDY FUNDING

Supported by NIH (U01-NS045911 and U01-NS045803).

DISCLOSURE

A. Cnaan is funded by NIH grants 2U01-NS045911, UL1RR031988, P30HD040677, P50AR060836, R01AR061875, and R01HD058567, and Department of Defense grant W81XWH-12-1-0417. S. Shinnar is funded by NIH grants R37-NS043209, 2U01-NS045911, U10NS077308, and 1U01NS088034, an NIH grant, and a grant from the Rett Syndrome research Trust; serves on the editorial board of *Pediatric Neurology* and on 2 DSMBs for UCB Pharma; has received personal compensation for serving on scientific advisory boards for Accorda, AstraZeneca, and Upsher Smith, and for consulting for Accorda, Neurelis, Upsher-Smith, and Zeris; has received royalties from Elsevier for co-editing *Febrile Seizures*; and has given expert testimony in medico-legal cases. R. Arya is funded by NIH grant 2U01-NS045911. P.C. Adamson reports no disclosures relevant to the manuscript. P. Clark is funded by NIH grants 2U01-NS045911 and U10-NS077311 and has received consulting and speaking fees from Eisai and Supernus. D. Dlugos is funded by NIH grants 1R01NS053998, 2U01NS045911, 1R01LM011124, and U01NS077276, the Epilepsy Study Consortium, the Pennsylvania Department of Health, and by prestudy protocol development agreements with Insys Therapeutics, Vanda Pharmaceuticals, and Ultragenyx; and has given expert testimony in medico-legal cases. D. Hirtz reports no disclosures relevant to the manuscript. D. Masur is funded by NIH grants R01-NS043209 and 2U01-NS045911 and has given expert testimony in medico-legal cases. T. Glauser is funded by NIH grants 2U01-NS045911, U10-NS077311, R01-NS053998, R01-NS062756, R01-NS043209, R01-LM011124, and R01-NS065840; has received consulting fees from Supernus, Sunovion, Eisai, UCB, Lundbeck, and Questcor; served as an expert consultant for the US Department of Justice; has received compensation for work as an expert on medico-legal cases; and receives royalties from a patent license from AssureX Health. Go to Neurology.org for full disclosures.

Received May 1, 2016. Accepted in final form October 4, 2016.

REFERENCES

1. Glauser TA, Cnaan A, Shinnar S, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. N Engl J Med 2010;362:790–799.
2. Glauser TA, Cnaan A, Shinnar S, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy: initial monotherapy outcomes at 12 months. Epilepsia 2013;54:141–155.
3. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342:314–319.
4. Brodie MJ, Barry SJ, Bamagous GA, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. Neurology 2012;78:1548–1554.
5. Arts WF, Brouwer OF, Peters AC, et al. Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch study of epilepsy in childhood. Brain 2004;127:1774–1784.
6. Mattson RH, Cramer JA, Collins JF. A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults: The Department of Veterans Affairs Epilepsy Cooperative Study No. 264 Group. N Engl J Med 1992;327:765–771.
7. Richens A, Davidson DL, Cartlidge NE, Easter DJ. A multicentre comparative trial of sodium valproate and carbamazepine in adult onset epilepsy: Adult EPITEG Collaborative Group. J Neurol Neurosurg Psychiatry 1994;57:682–687.
8. Kwan P, Brodie MJ. Epilepsy after the first drug fails: substitution or add-on? Seizure 2000;9:464–468.
9. Elkis LC, Bourgeois B, Wyllie E, Kotagal P. Efficacy of second antiepileptic drug after failure of one drug in children with partial epilepsy. Epilepsia 1993;34:107.
10. Camfield PR, Camfield CS, Gordon K, Dooley JM. If a first antiepileptic drug fails to control a child's epilepsy, what are the chances of success with the next drug? J Pediatr 1997;131:821–824.
11. Berg AT, Levy SR, Testa FM, Blumenfeld H. Long-term seizure remission in childhood absence epilepsy: might initial treatment matter? Epilepsia 2014;55:551–557.
12. Berg AT, Rychlik K. The course of childhood-onset epilepsy over the first two decades: a prospective, longitudinal study. Epilepsia 2015;56:40–48.
13. Masur D, Shinnar S, Cnaan A, et al. Pretreatment cognitive deficits and treatment effects on attention in childhood absence epilepsy. Neurology 2013;81:1572–1580.
14. Conners C. Conners' Continuous Performance Test II: Technical Guide and Software Manual. North Tonawanda, NY: Multi-Health Systems; 2002.
15. Fleming TR, Harrington DP. A class of hypothesis tests for one and two samples censored survival data. Commun Stat Theory Methods 1981;10:763–794.
16. Gares V, Andrieu S, Dupuy JF, Savy N. An omnibus test for several hazard alternatives in prevention randomized controlled clinical trials. Stat Med 2015;34:541–557.
17. Glauser T, Ben-Menachem E, Bourgeois B, et al. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 2006;47:1094–1120.
18. Report of the ILAE Commission on Antiepileptic Drugs. Considerations on designing clinical trials to evaluate the place of new antiepileptic drugs in the treatment of newly diagnosed and chronic patients with epilepsy. Epilepsia 1998;39:799–803.
19. Cox DR. Regression models and life-tables. J R Stat Soc Ser B 1972;34:187–220.
20. Harrington DP, Fleming TR. A class of rank test procedures for censored survival data. Biometrika 1982;69:553–566.
21. Wasserstein RL, Lazar NA. The ASA's Statement on p-values: context, process, and purpose. Am Stat 2016;70:129–133.
22. Shinnar S, Cnaan A, Hu F, et al. Long-term outcomes of generalized tonic-clonic seizures in a childhood absence epilepsy trial. Neurology 2015;85:1108–1114.
23. Mohanraj R, Brodie MJ. Outcomes in newly diagnosed localization-related epilepsies. Seizure 2005;14:318–323.
24. Ramos-Lizana J, Aguilera-Lopez P, Aguirre-Rodriguez J, Cassinello-Garcia E. Response to sequential treatment schedules in childhood epilepsy: risk for development of refractory epilepsy. Seizure 2009;18:620–624.
25. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51:1069–1077.

© 2016 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.