Long-term outcomes of generalized tonic-clonic seizures in a childhood absence epilepsy trial

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ABSTRACT

Objective: To determine incidence and early predictors of generalized tonic-clonic seizures (GTCs) in children with childhood absence epilepsy (CAE).

Methods: Occurrence of GTCs was determined in 446 children with CAE who participated in a randomized clinical trial comparing ethosuximide, lamotrigine, and valproate as initial therapy for CAE.

Results: As of June 2014, the cohort had been followed for a median of 7.0 years since enrollment and 12% (53) have experienced at least one GTC. The median time to develop GTCs from initial therapy was 4.7 years. The median age at first GTC was 13.1 years. Fifteen (28%) were not on medications at the time of their first GTC. On univariate analysis, older age at enrollment was associated with a higher risk of GTCs ($p = -0.0009$), as was the duration of the shortest burst on the baseline EEG ($p = 0.037$). Failure to respond to initial treatment ($p < 0.001$) but not treatment assignment was associated with a higher rate of GTCs. Among patients initially assigned to ethosuximide, 94% (15/16) with GTCs experienced initial therapy failure ($p < 0.0001$). A similar but more modest effect was noted in those initially treated with valproate ($p = 0.017$) and not seen in those initially treated with lamotrigine.

Conclusions: The occurrence of GTCs in a well-characterized cohort of children with CAE appears lower than previously reported. GTCs tend to occur late in the course of the disorder. Children initially treated with ethosuximide who are responders have a particularly low risk of developing subsequent GTCs. **Neurology® 2015;85:1108–1114**

GLOSSARY

AED = antiepileptic drug; **CAE** = childhood absence epilepsy; **CI** = confidence interval; **GTC** = generalized tonic-clonic seizure; **HR** = hazard ratio; **IQR** = interquartile range; **JAE** = juvenile absence epilepsy; **RCT** = randomized controlled trial.

Childhood absence epilepsy (CAE) is the most common childhood-onset epilepsy syndrome, accounting for 10%–17% of all childhood-onset epilepsy.^{1,2} Although the core seizure type in CAE is absence seizures, studies have reported that generalized tonic-clonic seizures (GTCs) occur in 30%–60% of children with CAE.^{3,4} Lack of clarity about the homogeneity of these reports' study populations means the incidence of GTCs remains unclear. The timing of GTC onset in children with CAE is also imprecise but GTCs tend to occur late in the course of CAE with latencies of 5–10 years after syndrome onset.^{3,4}

A double-blind randomized controlled trial (RCT) of initial therapy for children with CAE enrolled 446 children with newly diagnosed CAE (without a history of GTCs) and randomized them to ethosuximide, lamotrigine, or valproate.^{5,6} This cohort was well-characterized with pretreatment and subsequent prospective longitudinal assessment of seizure status, EEG, cognition, and behavioral status. The RCT identified ethosuximide as the optimal initial therapy due to superior efficacy compared with lamotrigine and similar efficacy but fewer attentional side effects when compared to valproic acid.^{5,6} The results of this RCT have altered clinical practice recommendations.^{7,8} However, unlike lamotrigine and valproic acid, which are

Supplemental data
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Coinvestigators are listed on the *Neurology*® Web site at Neurology.org.

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considered effective against GTCs,⁷ ethosuximide is not considered effective in the treatment of GTCs. Therefore, a concern about using ethosuximide as first-line therapy for CAE is whether using it will be associated with a higher risk of subsequent GTCs. This report presents data on the long-term incidence and early predictors of GTCs from the CAE trial.

METHODS Participant population. In a prospective double-blind efficacy/effectiveness RCT, 446 children with newly diagnosed CAE were randomized equally to ethosuximide, valproate, or lamotrigine. Details of the RCT's inclusion/exclusion criteria were published previously.^{5,6} Study participants had only absence seizures at the time of study entry; a GTC prior to starting study medication was an exclusion criterion.

Study design. A detailed methodology for the efficacy/effectiveness RCT was published previously.^{5,6} The primary outcome of the double-blind portion of the study was freedom from treatment failure (i.e., complete seizure freedom without intolerable side effects) determined at the week 16–20 visit. Absence seizure status was assessed both clinically and by EEG at that visit. As is customary in these types of studies, the occurrence of a GTC at any time during the RCT was assessed through clinical history. No specific additional tests were performed to confirm the occurrence of a GTC. No systematic data were collected on the number of GTCs, although most participants had few. If treatment was successful at the week 16–20 visit, participants continued on their initial therapy until 24 months of seizure freedom were observed, and then, following a normal EEG or EEG with minor findings (e.g., sharply contoured slowing during hyperventilation, asymmetric driving during photic stimulation, centroposterior sharp waves with a dipole), weaned off study medication.⁵ If unsuccessful on initial therapy, participants were treated with other therapies.

Participants who participated in the RCT were offered the opportunity to continue in a long-term follow-up phase. The first visit in the follow-up phase gathered all seizure history (including the occurrence of GTCs) that happened since the last RCT visit. Long-term follow-up study visits were scheduled at 3-month intervals and captured the interval seizure history (including GTCs and medication history) since the last study visit.

Data capture included baseline characteristics as well as treatment assignment, freedom from failure, and seizure status at the week 16–20 visit (the RCT's primary endpoint), age at first GTC, and antiepileptic drugs (AEDs) taken at the time of first GTC.

Statistical methods. The number of GTCs by initial treatment and grouped age (≤ 6 years old, 7–8 years old, 9 years and older) was compared using a χ^2 test. Cumulative incidence calculations were based on time since randomization until the first GTC and observations were censored at last follow-up for those not developing a GTC. Time to GTC failure event curves were compared using a log-rank test. Cox proportional hazards models assessed whether baseline characteristics beyond treatment and age, e.g., other demographics, neuropsychological and EEG parameters, predicted GTCs. In addition, freedom from treatment failure and seizure freedom outcomes at the week 16–20 visit were explored as predictors of GTCs after the week 16–20 visit, excluding patients who had GTCs prior to the week 16–20 visit. Seizure status for patients who discontinued prior to the week 16–20 visit, not due to a GTC, was defined as last known seizure status, based on the last EEG performed. Sensitivity analyses for seizure status excluded

these patients as seizure control was not expected until potentially the week 16–20 visit. Best-fitting most parsimonious models were fit. Additional secondary models used age, rather than time from randomization, as the time metric.

Standard protocol approvals, registrations, and patient consents. This study was approved by the institutional review boards of all 32 participating sites. Written parental informed consent and child assent (when appropriate) was obtained from all participants. The RCT was conducted under a Food and Drug Administration–approved investigational newdrug application. The study is listed at <http://clinicaltrials.gov/> under ClinicalTrials.gov identifier NCT00088452.

RESULTS Overall risk of developing GTCs. All 446 participants randomized in the RCT^{5,6} were included. As of June 2014, the cohort had been followed for a median of 7.0 years (interquartile range [IQR] 3.1–7.9 years), with 53 (12%) participants experiencing GTCs. This includes 16, 17, and 20 participants initially assigned to ethosuximide, valproic acid, and lamotrigine, respectively ($p = 0.67$). There are no differences in pretreatment demographics between the patients who developed GTCs and those who did not (table 1) except for age at entry, with the patients who developed GTCs being older on average.

The risk of developing GTCs overall, by initial drug assignment and by age group, is shown in figure 1, A–C. The median time to develop GTCs from randomization was 4.7 years (IQR 2.3–6.3). The median age at first GTC was 13.1 years. The cumulative risk for developing GTCs at 5 years following randomization is 8.5% (95% confidence interval [CI] 6.1%–12%) (figure 1A). There are no differences based on initial drug assignment (figure 1B).

Effect of age. The effect of age at randomization on the risk of GTCs is shown in figure 1C and table 1. Children with an older age at study entry had a higher risk of developing GTCs ($p = 0.0009$). For children with age at study entry ≥ 9 years, the cumulative risk of developing GTCs by 5 years after randomization was 19% (95% CI 12%–28%) compared with 3.9% (95% CI 1.7%–8.5%) ($p = 0.0003$) for those with age at study entry ≤ 6 years and 6% (95% CI 3%–13%) ($p = 0.030$) for those with age 7–8 years at study entry (figure 1B). Figure 2 shows a smoothed estimation of the hazards to develop a GTC for the 3 age groups within 5 years after randomization.

The age at which GTCs occurred was correlated with the age at study entry (figure 3) with a Pearson correlation coefficient of 0.59. The fitted regression model produces the following relationship:

$$\begin{aligned} \text{Age at first GTC} &= 6.523 + 0.87 \times \text{age at study entry} \\ &\quad (95\% \text{ CI for intercept } 5.516\text{--}7.531 \\ &\quad \text{and for slope } 0.744\text{--}0.997), \end{aligned}$$

confirming that the onset of GTCs is typically well into the course of the absence epilepsy regardless of

Table 1 Baseline demographic, pretreatment characteristics, initial therapy, and response of patients who did and did not develop a GTC

Characteristics	Participants without GTC (n = 393)	Participants with GTC (n = 53)	Total participants (n = 446)	p Value
Demographics and pretreatment characteristics at study entry				
Age at randomization, y, mean (SD)	7.5 (2.1)	8.6 (2.4)		0.0044
Age group at randomization, y, n (%)				
≤6	173 (44)	13 (25)	186 (42)	0.0022
7–8	120 (31)	15 (28)	135 (30)	
≥9	100 (25)	25 (47)	125 (28)	
Female, n (%)	226 (57)	28 (53)	254 (57)	0.52
Race, n (%)				
White	289 (74)	42 (79)	331 (74)	0.37
Black or African American	76 (19)	10 (19)	86 (19)	
Other	28 (7)	1 (2)	29 (7)	
Hispanic Latino	90 (23)	10 (19)	100 (22)	0.54
EEG shortest burst duration, s, mean (SD; n)	9.67 (7.2; 388)	7.62 (5.2; 52)	9.43 (7.0; 440)	0.012
Full-scale IQ, n, mean (SD; n)	95.24 (15.6; 349)	93.17 (13.7; 47)	94.99 (15.4; 396)	0.34
CPT confidence index, mean (SD; n)	55.54 (24.8; 350)	52.42 (23.8; 49)	55.16 (24.7; 399)	0.40
CPT confidence index ≥60, n (%)	126/350 (36)	16/49 (33)	142/399 (36)	0.75
WCST, perseverative responses, mean (SD; n)	94.62 (15.2; 220)	98.88 (13.3; 34)	95.19 (15.0; 254)	0.09
Initial double-blind treatment and outcome, n (%)				
Initial double-blind treatment				
Ethosuximide	138 (35)	16 (30)	154 (35)	0.67
Lamotrigine	126 (32)	20 (38)	146 (33)	
Valproic acid	129 (33)	17 (32)	146 (33)	
Treatment failure at week 16–20 visit	196 (50)	41 (77)	237 (53)	0.00019
Not seizure-free at week 16–20 visit	164 (42)	35 (66)	199 (45)	0.0011

Abbreviations: CPT = Connor Continuous Performance Test; GTC = generalized tonic-clonic seizure.

The p values are based on a Fisher exact test and for race an exact χ^2 test was used.

the age at onset. In addition, it means that those with an older age at onset develop GTCs after a shorter period of time than those who entered the study at a younger age.

The cumulative risk of developing GTCs as a function of age independent of when the child entered the study was examined (figure 2). For example, the cumulative risk of developing GTCs was 2.8% (95% CI 1.5%–5%), 15% (95% CI 11%–21%), and 24% (95% CI 17%–32%) at 10, 15, and 18 years, respectively.

Effect of medications. There was no difference in the rate of GTCs by initial treatment assignment (table 1, figure 1B). As GTCs tend to occur late, many children were no longer on the initial drug. At time of their first GTC, 7 participants were on ethosuximide (4 during the RCT and 3 during long-term follow-up), 13 were on valproic acid (6 during the RCT and 7 during long-term follow-up), and 4 were on lamotrigine (1 during the RCT and 3 during long-term follow-up). An additional 9 participants had GTCs after the RCT and were on

polytherapy (a surrogate for intractability) including at least 1 of the 3 study drugs, 5 were on other AEDs, and 15 were not receiving AEDs.

The median time off AEDs for 14 of the 15 participants no longer receiving AEDs was 2.0 years (IQR 0.7–4.1 years, one patient's data not available). Nine (60%) of the 15 patients completed 2 years of freedom from failure on study treatment and were weaned off AEDs per the study protocol. Six (40%) of the 15 patients who had GTCs while off medication experienced treatment failure during the RCT. While 13 of the 15 participants did not have absence seizures on their last study EEG, 2 did. In 1 case, the last EEG was 2 years before the GTC, and in another case (an 18-year-old patient) the patient wanted to wean off medication at the 6-year visit despite the last EEG not being seizure-free. The patient had a GTC 3 months after discontinuing medication; lamotrigine treatment was resumed after the GTC.

Other baseline parameters. Sex, race, and ethnicity had no association with the risk of a GTC (table 1) or

Figure 1 Overall cumulative incidence curves and confidence bands

Overall cumulative incidence curve and confidence band of time to development of generalized tonic-clonic seizures (GTCs) overall (A), by initial drug assignment (log-rank test $p = 0.8$, B), and by age group (log-rank test $p = 0.0009$). ETX = ethosuximide; LTG = lamotrigine; VPA = valproic acid.

time to GTC. Neuropsychological variables⁹ such as full-scale IQ, the Confidence Index on the Connors' Continuous Performance Text, and the number of

perseverative errors on the Wisconsin Card Sorting Test also had no association with the risk of developing a GTC (tables 1 and 2). In contrast, duration of shortest burst on EEG, which was associated with a differential rate of freedom from failure at week 16–20 visit,¹⁰ was also associated with a modest association with the risk of developing a GTC (hazard ratio [HR] 0.939, 95% CI 0.886–0.996, see table 2), with shorter duration being associated with a higher risk of developing GTCs.

Effect of response to initial therapy. Response to initial treatment was strongly associated with the risk of subsequent GTCs (table 2). Eight participants had a GTC prior to the week 16–20 visit and are excluded from this analysis. Patients who had a treatment failure at the week 16–20 visit or earlier for reasons other than a GTC had a markedly increased risk of subsequently developing GTCs (HR 3.05, 95% CI 1.58–5.91). In children who had a treatment failure by the week 16–20 visit, the cumulative risk of developing GTCs by 5 years after randomization was 11% (95% CI 7%–16%), compared with 3.6% (95% CI 1.6%–7.8%) ($p = 0.005$) in those who met the freedom from failure criterion at the week 16–20 visit. A similar effect was observed when looking at seizure freedom. Patients who were not seizure-free at the week 16–20 visit had a HR of 2.3 as compared to those who were seizure-free at that time (table 2).

Among the 16 GTCs that occurred in patients initially assigned to ethosuximide (see table 1), only 1 occurred in a patient whose ethosuximide treatment was successful. All 15 other GTCs occurred in patients who had ethosuximide treatment failure at the week 16–20 visit ($p < 0.0001$ for association between week 16–20 status and GTC status within the ethosuximide group). Among the 17 GTCs that occurred in patients originally assigned to valproic acid, 5 occurred in patients in whom valproic acid was successful at the week 16–20 visit and 12 in whom valproic acid was a failure ($p = 0.017$). Among the 20 GTCs that occurred on lamotrigine, 6 occurred in patients for whom lamotrigine was successful at the week 16–20 visit and 14 in whom lamotrigine was a failure ($p = 1.0$), which is comparable to the 29% treatment success rate of lamotrigine in the trial.⁶ Therefore, the overall relationship between week 16–20 visit status and GTC is primarily derived from that relationship in ethosuximide and valproic acid, which was particularly striking in the ethosuximide group. Within the lamotrigine group alone, week 16–20 visit success or failure status is not a predictor of developing a GTC.

Multivariable analysis of risk factors. On univariate analysis, baseline factors associated with a differential risk of GTCs included only age at randomization and

Figure 2 Cumulative risk and confidence band of developing generalized tonic-clonic seizures (GTCs) as a function of age without consideration of age at randomization or response to initial therapy

the duration of shortest burst on the baseline EEG. Additional factors included freedom from failure and seizure freedom status at the week 16–20 visit (table 2). On multivariable analysis (table 2), age at entry, freedom from failure, and seizure freedom status at the week 16–20 visit remained significant and at approximately the same order of magnitude as in the univariate analysis. Each increase of age by 1 year at diagnosis confers approximately a 20% increase in the HR to develop a GTC. When age at study entry is included in the model, the effect of the shortest burst duration on EEG is no longer significant. Having

Figure 3 Relationship between age at randomization and age at generalized tonic-clonic seizure (GTC) in those patients who had a GTC

failed the initial treatment confers a roughly 3-fold increase in the HR for a GTC, and not being seizure-free at the week 16–20 visit confers a roughly 2.3-fold increase in the HR for a GTC. These results remain when excluding the patients who discontinued ($n = 105$, mostly due to side effects) prior to the week 16–20 visit.

DISCUSSION Consistent with earlier reports,^{2,3} the occurrence of GTCs in CAE is a relatively late phenomenon. The overall risk of GTCs in this well-characterized cohort of patients with CAE is lower than that reported in earlier series (12% vs 30–60%). This may be due to a variety of factors, including the duration of follow-up. GTCs tended to occur 5–10 years after onset and this cohort has been followed for a median of 7.0 years. Another key reason is that in this study, children with juvenile absence epilepsy (JAE), which is associated with a much higher rate of GTCs¹¹ and had been included in some earlier studies, were excluded. While we excluded children with CAE who presented with GTCs, this was a rare event both in this study and the published literature,^{1–4} so it is unlikely to have significantly altered our estimates of the occurrence of GTCs.

Among baseline characteristics, older age at onset and shortest burst duration on baseline EEG are associated with a higher risk of GTCs. This is interesting as JAE, which has an older but overlapping age at onset of 7–17 years, is associated with a very high risk of developing GTCs.¹¹ We have followed the cohort long enough that it is clear that this is not simply that the GTCs are occurring at an older age, which will not be achieved until much longer follow-up in those with younger age at onset, but that it also is a function of the age at onset. The EEG parameter is also associated with a differential rate of treatment response at the week 16–20 visit and of attentional problems.¹⁰ Interestingly, the participants with a shorter duration of shortest EEG burst have a lower treatment success rate and a higher risk of developing GTCs, but a lower rate of attentional problems. This suggests, as we have previously postulated,^{9,10} that specific features of the EEG may serve to identify subtypes of CAE. However, the effect of this EEG variable disappears once effect of treatment response is accounted for.

The risk of developing GTCs does not appear to be a function of initial treatment assignment and was not different in the ethosuximide arm vs the other 2 treatment arms. However, the risk of developing GTCs is strongly a function of treatment response at the week 16–20 visit, with responders less likely to develop GTCs. This is paradoxical as the treatment response is much lower in those assigned to lamotrigine than those assigned to ethosuximide and valproic acid. The apparent contradiction is explained by

Table 2 Associations between baseline variables and treatment response and occurrence of generalized tonic-clonic seizures

Parameter	No.	Parameter estimate	Standard error	p Value	Hazard ratio	95% confidence limits
Single variable models						
Age at enrollment	446	0.22	0.064	0.0005	1.246	1.10-1.412
Pretreatment full-scale IQ	396	-0.012	0.0096	0.21	0.988	0.97-1.007
Pretreatment CPT confidence index	399	-0.0026	0.00583	0.66	0.997	0.986-1.009
WCST, perseverative responses	254	0.019	0.0117	0.1	1.019	0.996-1.043
Pretreatment EEG shortest burst duration	440	-0.062	0.0299	0.037	0.939	0.886-0.996
Initial double-blind treatment with lamotrigine	446	0.19	0.336	0.57	1.211	0.628-2.339
Initial double-blind treatment with valproic acid	446	0.041	0.349	0.91	1.042	0.526-2.063
Treatment failure at week 16-20 visit	438	1.12	0.337	0.0009	3.052	1.576-5.913
Not seizure-free at week 16-20 visit	438	0.83	0.3	0.0061	2.304	1.268-4.186
Two variable models: all pairs of significant variables						
Pretreatment EEG shortest burst duration	440	-0.05	0.0285	0.079	0.951	0.90-1.006
Age at enrollment	440	0.2	0.066	0.0023	1.223	1.075-1.391
Treatment failure at week 16-20 visit	432	1.15	0.349	0.001	3.155	1.592-6.253
Pretreatment EEG shortest burst duration	432	-0.086	0.0381	0.025	0.918	0.852-0.989
Not seizure-free at week 16-20 visit	432	0.81	0.31	0.009	2.253	1.225-4.144
Pretreatment EEG shortest burst duration	432	-0.085	0.037	0.0216	0.918	0.854-0.988
Treatment failure at week 16-20 visit	438	1.1	0.338	0.0011	3.017	1.557-5.846
Age at enrollment	438	0.2	0.068	0.0028	1.226	1.073-1.401
Not seizure-free at week 16-20 visit	438	0.81	0.3	0.0076	2.26	1.242-4.103
Age at enrollment	438	0.2	0.068	0.003	1.224	1.071-1.398

Abbreviations: CPT = Connor Continuous Performance Test; WCST = Wisconsin Card Sorting Test.

a closer look at the data. The rate of developing GTCs is strikingly lower in treatment responders than non-responders in the ethosuximide group, moderately lower in responders in the valproic acid group, but not different in responders vs nonresponders in the lamotrigine group. It is difficult to know at this time whether the striking reduction in the risk of developing GTCs in those assigned to ethosuximide (even many years later when off the medication) represents a disease modification effect, as was suggested by an observational study¹² and by animal data.^{13,14} Longer duration of follow-up with focus on remission outcomes is in progress and may provide a more definitive answer. However, the data provide compelling evidence that concern about the occurrence of GTCs should not change the status of ethosuximide as the preferred first-line therapy for CAE.^{5,6} These results are specific to CAE and are not necessarily generalizable to other absence syndromes such as JAE where the risk of GTCs is much higher.¹¹

An unexpected finding was the substantial number of children who were off medications at the time of the first GTC. Even if the 2 participants who discontinued medications while not seizure-free are excluded, there are still 13 participants who were

seizure-free at last EEG and off medications when they developed GTCs. Longer term follow-up of this cohort will provide a better estimate of how often this occurs and whether it represents evolution of the CAE syndrome to a different primary generalized epilepsy with age¹⁵ or a different phenomenon.

The occurrence of GTCs in a well-characterized cohort of children with CAE appears lower than previously reported. Age at onset, baseline EEG parameters, and response to initial therapy are associated with a differential risk of developing GTCs. The GTCs tend to occur late in the course of the disorder and may occur in children thought to be in remission who are off medication. Children initially treated with ethosuximide who are responders have a particularly low risk of developing subsequent GTCs.

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: S. Shinnar, A. Cnaan, F. Hu, P. Clark, D. Dlugos, D.G. Hirtz, D. Masur, E. Mizrahi, S. Moshé, T.A. Glauser. Statistical analysis: A. Cnaan. Dr. Shinnar wrote the first draft of the manuscript. Drs. Shinnar, Cnaan, Dlugos, Hirtz, Masur, Mizrahi, Moshé, and Glauser, along with F. Hu and P. Clark, 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.

STUDY FUNDING

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

DISCLOSURE

S. Shinnar is funded by NIH grants NS 2R01-NS043209, 2U01-NS045911, U10NS077308, and P20 NS080181. He serves on the Editorial Board of *Pediatric Neurology* and on a DSMB for UCB Pharma. He has received personal compensation for serving on Scientific Advisory Boards for Accordia, AstraZenica, Questcor, and Upsher Smith, and for consulting for Accordia, Questcor, and Upsher-Smith. He has received royalties from Elsevier for coediting the book *Febrile Seizures*. He has also given expert testimony in medico-legal cases. A. Cnaan is funded by NIH grants 2U01-NS045911, UL1RR031988, P30HD040677, P50AR060836, R01AR061875, R01HD058567, Department of Defense grant, and Department of Education grant H133B090001. F. Hu is funded by NIH grants 2U01-NS045911, P30HD040677, P50AR060836, R01AR061875, R01HD058567, Department of Defense grant W81XWH-09-1-0592, and Department of Education grant H133B090001. P. Clark is funded by NIH grants 2U01-NS045911 and U10-NS077311. She has received consulting and speaking fees from Eisai. D. Dlugos is funded by NIH grants 1R01NS053998, 2U01NS045911, 1R01LM011124, and U01NS077276, by the Epilepsy Study Consortium, and by a prestudy protocol development agreement with Insys Therapeutics. She has also 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. He has also given expert testimony in medico-legal cases. E. Mizrahi is funded by NIH grant U01-NS045911, Department of Defense grant W81XWH-08-2-0149, and NeuroPace, Inc. (Responsive Neurostimulator System Long-Term Treatment Clinical Investigation). He receives royalties from UpToDate, McGraw-Hill Medical Publishers, and Wolters Kluwer Publishers. He serves as chair, scientific advisory board of Treatment of Neonatal Seizures with Medical Off-Patient (NEMO), funded by European Union and on review panels for NIH and US Food and Drug Administration. S. Moshé is the Charles Frost Chair in Neurosurgery and Neurology and funded by grants from NIH NS43209, NS20253, NS45911, NS-78333, CURE, US Department of Defense, UCB, and the Heffer Family and Siegel Family Foundations. He receives annual compensation from Elsevier for his work as Associate Editor on *Neurobiology of Disease* and royalties from 2 books he co-edited. He received a consultant fee from Lundbeck and UCB. T. Glauser is funded by NIH grants 2U01-NS045911, U10-NS077311, R01-NS053998, R01-NS062756, R01-NS043209, R01-LM011124, and R01-NS065840. He has received consulting fees from Supernus, Sunovion, Eisai, UCB, Lundbeck, and Questcor. He also serves as an expert consultant for the US Department of Justice and has received compensation for work as an expert on medico-legal cases. He receives royalties from a patent license from AssureRx Health. Go to Neurology.org for full disclosures.

Received December 31, 2014. Accepted in final form June 4, 2015.

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