Evidence-based guideline update: Medical treatment of infantile spasms

Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society

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ABSTRACT

Objective: To update the 2004 American Academy of Neurology/Child Neurology Society practice parameter on treatment of infantile spasms in children.

Methods: MEDLINE and EMBASE were searched from 2002 to 2011 and searches of reference lists of retrieved articles were performed. Sixty-eight articles were selected for detailed review; 26 were included in the analysis. Recommendations were based on a 4-tiered classification scheme combining pre-2002 evidence and more recent evidence.

Results: There is insufficient evidence to determine whether other forms of corticosteroids are as effective as adrenocorticotrophic hormone (ACTH) for short-term treatment of infantile spasms. However, low-dose ACTH is probably as effective as high-dose ACTH. ACTH is more effective than vigabatrin (VGB) for short-term treatment of children with infantile spasms (excluding those with tuberous sclerosis complex). There is insufficient evidence to show that other agents and combination therapy are effective for short-term treatment of infantile spasms. Short lag time to treatment leads to better long-term developmental outcome. Successful short-term treatment of cryptogenic infantile spasms with ACTH or prednisolone leads to better long-term developmental outcome than treatment with VGB.

Recommendations: Low-dose ACTH should be considered for treatment of infantile spasms. ACTH or VGB may be useful for short-term treatment of infantile spasms, with ACTH considered preferentially over VGB. Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to VGB in infants with cryptogenic infantile spasms, to possibly improve developmental outcome. A shorter lag time to treatment of infantile spasms with either hormonal therapy or VGB possibly improves long-term developmental outcomes. *Neurology*® 2012;78:1974-1980

GLOSSARY

AAN = American Academy of Neurology; **ACTH** = adrenocorticotrophic hormone; **AE** = adverse effect; **AED** = antiepileptic drug; **BD** = Breslow-Day; **CI** = confidence interval; **ERG** = electroretinogram; **FDA** = Food and Drug Administration; **IVIg** = IV immunoglobulin; **LEV** = levetiracetam; **NZP** = nitrazepam; **OR** = odds ratio; **RCT** = randomized controlled trial; **TPM** = topiramate; **TRH** = thyrotropin-releasing hormone; **TSC** = tuberous sclerosis complex; **UKISS** = United Kingdom Infantile Spasms Study; **VABS** = Vineland Adaptive Behavioral Scale; **VGB** = vigabatrin; **VPA** = valproic acid; **ZNS** = zonisamide.

Supplemental data at
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Supplemental Data

CME

Infantile spasms constitute a unique, age-specific epilepsy syndrome of early infancy characterized by epileptic spasms often accompanied by neurodevelopmental regression and an EEG finding of hypsarrhythmia. When all 3 components are present, the eponym “West syndrome” is commonly used. The incidence is 2–3 per 10,000 live births^{1,2}; the lifetime prevalence rate is 1.5–2 per 10,000 children.³ Infantile spasms are slightly

more common in males, and a family history exists in 3%–6% of cases. The spontaneous remission rate of infantile spasms described in limited natural history studies is 30%.^{4,5} A 2004 American Academy of Neurology (AAN)/Child Neurology Society parameter on the medical treatment of infantile spasms⁶ concluded that adrenocorticotrophic hormone (ACTH) is probably an effective agent for short-term treatment of infantile

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Appendices e-1–e-6, references e1–e38, and tables e-1–e-5 are available on the *Neurology*® Web site at www.neurology.org.

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spasms (Level B). The 2004 parameter also concluded that vigabatrin (VGB) is possibly effective for short-term treatment of infantile spasms (Level C) and for treatment of children with tuberous sclerosis (Level C). In children with infantile spasms and tuberous sclerosis, 2 Class III studies^{7,8} from the 2004 practice parameter (combined $n = 28$) showed spasms cessation at 2–3 weeks in 16 of 28 (57%) patients treated with VGB, with overall response rate of 100% in both studies. Therefore, VGB is possibly effective for short-term treatment of infantile spasms in the majority of children with tuberous sclerosis (Level C). Data were insufficient at that time to recommend other antiepileptic drugs (AEDs), the ketogenic diet, pyridoxine, or IV immunoglobulin (IVIg) for short-term treatment of infantile spasms or to assess the impact of treatment on long-term outcomes.

In August 2009, the US Food and Drug Administration (FDA) approved VGB for use in infantile spasms and as add-on therapy for refractory seizures.⁹ Since 2004, only one study provided evidence higher than Class IV, a single large Class III randomized controlled trial (RCT) comparing low-dose and high-dose VGB for treatment of infantile spasms.¹⁰ This study showed more patients in the high-dose group achieved spasms cessation within 14 days relative to those in the low-dose VGB group (15.9% vs 7%; $p = 0.03$). In the symptomatic tuberous sclerosis complex (TSC) subgroup, the spasm-free rate was higher in those allocated high-dose VGB (25% vs 16.7%). A post hoc analysis video-EEG performed at any subsequent visit showed hypsarrhythmia resolution in 30.8% of patients on high-dose VGB vs 13.2% on low-dose VGB.

Considerable variation remains in the management of infantile spasms. This is evident in the recently published US Consensus Report¹¹ and the various responses it drew.^{12,13} The agents used, dosage regimen, and treatment duration vary significantly among studies, which remain limited to small numbers of prospective trials and even fewer RCTs. Most published outcome measures are short-term and based on small numbers of patients. These variable practice patterns in treating infantile spasms and 8 years of an emerging body of literature on the subject have necessitated an update of the 2004 parameter. Therefore, we reviewed the literature to update the guideline with recommendations to address the following clinical questions for which previous data were insufficient:

1. Are other forms of corticosteroids as effective as ACTH for short-term treatment of infantile spasms?
2. Are low-dose ACTH regimens effective for short-term treatment of infantile spasms?

3. Is ACTH more effective than VGB for short-term treatment of infantile spasms?
4. Is there a role for the ketogenic diet or for AEDs other than VGB in managing infantile spasms?
5. Does the successful short-term treatment of infantile spasms lead to long-term improvement of neurodevelopmental outcomes or a decreased epilepsy incidence?

DESCRIPTION OF THE ANALYTIC PROCESS

An updated literature search of MEDLINE and EMBASE databases (2002–August 2011) using the OVID interface was conducted using the process described in the 2004 parameter (see appendix e-3 on the *Neurology*[®] Web site at www.neurology.org).⁶ The combined MEDLINE and EMBASE text word searches identified 1,935 articles. All search titles and abstracts were analyzed for content. English-language articles on therapy, prognosis, and adverse effects (AEs) were selected. Sixty-eight articles were chosen for detailed review; 26 were included in the analysis. Two panelists independently reviewed, abstracted, and classified the articles, to assess the quality of data related to study design and treatment effect. A third panelist arbitrated any disagreements in ratings. For each question, evidence is sequentially analyzed and then summarized to determine the overall strength of the evidence and to formulate recommendations.

Articles selected for detailed review required a clearly stated diagnosis of infantile spasms, an EEG demonstrating hypsarrhythmia or modified hypsarrhythmia (articles using routine EEG recording were included because not all articles used prolonged video-EEG monitoring), and inclusion of children aged 1–36 months. Infantile spasms were classified as either symptomatic (i.e., of known cause) or cryptogenic (of unknown cause but presumably genetic in many infants) as defined by the International League Against Epilepsy.¹⁴ Cases described as idiopathic were included in the cryptogenic group for analysis.

We excluded studies of children with Lennox-Gastaut syndrome, studies of children aged <1 month or >36 months at the time of study entry, and studies wherein an EEG was not initially performed to confirm the presence of hypsarrhythmia or modified hypsarrhythmia. Also excluded were retrospective studies with single case reports, case series containing fewer than 4 infants, studies on long-term prognosis that were uncontrolled for treatment, letters, abstracts, unpublished data, and review articles.

Analysis included short-term, intermediate, and long-term outcome measures. Short-term outcome measures were defined as complete spasms cessation; hypsarrhythmia resolution and, where documented, EEG normalization; and relapse rate. AEs and mortality

were documented. For studies with a mean follow-up of >12 months, intermediate to long-term outcome measures were EEG without epileptiform abnormalities, absence of seizures, and normal development. Data recorded included the number of patients entering and completing the trial, age at spasms onset, age at study entry, treatment lag (time of spasms onset to treatment initiation with the agents described herein), gender, etiology, drug dosage, therapy duration, cointerventions, and follow-up duration.

The Cochran-Mantel-Haenszel statistical method was used in the meta-analysis to quantify the clinical efficacy of ACTH vs VGB (question 3). This method is used to perform a stratified analysis when comparing odds ratios (OR) across studies. It combines the ORs while maintaining the group from which the data came. The Breslow-Day (BD) statistic is then applied to test the homogeneity of the OR across the strata. When the BD statistic is nonsignificant, all studies in the meta-analysis are pointing in the same direction, signifying concordance.

The AAN's 4-tiered article classification scheme for therapeutic evidence was used (appendix e-4); the strength of the recommendations was linked to the evidence (appendix e-5).

ANALYSIS OF EVIDENCE Short-term outcomes.

Other forms of corticosteroids. *Are other forms of corticosteroids as effective as ACTH for treatment of infantile spasms (table e-1)?*

Previously reviewed evidence. Five studies were identified in the 2004 parameter: 2 RCTs (1 Class II,¹⁵ 1 Class III¹⁶) using prednisone; 2 Class III prospective, open-label studies using prednisolone¹⁷ and prednisone¹⁸; 1 Class III prospective cohort series using liposteroid¹⁹; and 1 Class IV retrospective case series using prednisone.²⁰ Oral corticosteroid dose ranged from 2 to 3 mg/kg/day. The prospective Class II and III studies reported 29%–39% responder rates for spasms cessation.

Updated evidence. Three studies (n = range from 10 to 55) were included for analysis. One study, a large Class III RCT (n = 55), compared a high-dose oral prednisolone protocol (40–60 mg/day) with IM ACTH.²¹ This short-term study showed spasms responder rates of 76% for synthetic ACTH and 70% for prednisolone, with neither agent showing significant difference in the EEG response rate at 14 days ($p = 0.61$). A small, prospective Class IV case series (n = 10) using a course of pulse IV methylprednisolone for 3 days followed by a 2-month oral prednisolone taper showed spasms cessation and hypsarrhythmia resolution in 50% of patients within 14 days.²² In a small, retrospective Class IV study (n = 18), spasms resolution at treatment day 10 was better with ACTH than dexamethasone.²³

Conclusion. Data are insufficient regarding the equivalence of other corticosteroids to ACTH (Class III and IV evidence).

Recommendation. The evidence is insufficient to recommend the use of prednisolone, dexamethasone, and methylprednisolone as being as effective as ACTH for short-term treatment of infantile spasms (Level U).

Low-dose ACTH. *Are low-dose ACTH regimens effective for short-term treatment of infantile spasms (table e-2)?* The previous parameter identified 4 studies reporting use of low-dose ACTH: a Class I RCT²⁴ comparing high- and low-dose natural ACTH; a Class II RCT¹⁶ comparing low-dose natural ACTH with prednisone; a Class III RCT²⁵ comparing high- and low-dose synthetic ACTH; and a Class III prospective, open-label study of natural ACTH.²⁶ Response rates to low-dose ACTH in the RCTs varied from 42% to 75%. The doses and forms of ACTH used in these studies vary; however, the Class I RCT²⁴ (n = 50) comparing 150 IU/m² with 20 IU/day of natural ACTH showed no significant difference in clinical spasms cessation (50% vs 58%, respectively), hypsarrhythmia resolution (23% vs 21%, respectively), or relapse rates (or AEs) (15% vs 21%, respectively). The same low-dose natural ACTH was used in a Class II RCT¹⁶ (n = 12) showing an EEG and clinical response rate of 42% and relapse rate of 33%.

Conclusion. A Class I study showed similar efficacy between low-dose (20–30 IU) and high-dose (150 IU/m²) natural ACTH, and a Class II study using the same low-dose natural ACTH showed clinical and EEG response rates of >40%. The evidence suggests that low-dose ACTH is probably as effective as high-dose ACTH for short-term treatment of infantile spasms (Class I and II evidence).

Recommendation. Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms (Level B).

ACTH vs vigabatrin. *Is ACTH more effective than vigabatrin for short-term treatment of infantile spasms (table e-3)?*

Previously reviewed evidence. Two studies were identified in the 2004 parameter, a Class III RCT⁸ and a Class IV retrospective case series.²⁷ In the Class III study, which included patients with TSC, spasms cessation at 20 days of therapy occurred in 74% of patients given synthetic ACTH vs 48% of patients given VGB ($p = 0.12$). When data on patients with TSC are excluded, spasms cessation in patients allocated ACTH vs VGB is 72% vs 40%, respectively, with OR of 3.9 favoring ACTH (95% CI 0.99–15.27).

Updated evidence. Three studies (n = range from 28 to 107) met inclusion criteria. A large, multicenter Class III randomized controlled study (n = 107, excluding TSC cases) compared VGB with hormonal

therapy using high-dose synthetic ACTH or high-dose prednisolone.²¹ This study demonstrated better spasms-free outcomes for ACTH (76%) over VGB (54%) at 14 days, using an intention-to-treat analysis. Responder rates were similar for the symptomatic and cryptogenic groups. Resolution of hypsarrhythmia was 89% for ACTH vs 56% for VGB, but EEG was not performed in all cases at follow-up. AEs were reported in similar numbers for both treatment arms (ACTH = 44%, VGB = 54%). Outcome of the same 107 patients at age 14 months²⁸ showed the proportion of infants with spasms cessation without subsequent relapse was similar in the 2 treatment arms (hormonal therapy = 40%, VGB = 37%; $p = 0.71$).

A meta-analysis comparing the clinical response of synthetic ACTH with that of VGB in 2 Class III studies^{8,21} excluding patients with TSC was performed using the Cochran-Mantel-Haenszel statistical methodology to produce combined OR for the 2 studies. The overall OR of spasms cessation using ACTH was 3.10 (95% confidence interval [CI] 1.34–7.20, $p = 0.0076$), indicating ACTH was 3 times more likely than VGB to result in spasms cessation. The B-D statistic ($p = 0.68$) for the homogeneity of the ORs was nonsignificant, indicating concordance.

A small Class III study ($n = 9$) comparing high-dose natural ACTH with VGB²⁹ showed no significant difference, with all patients in both treatment arms responding. All patients had resolution of clinical spasms and hypsarrhythmia after 2 weeks of either treatment arm, although 5 of the 9 patients continued to have moderate to severely abnormal EEGs and were crossed over to the alternate drug.

Conclusion. Two Class III studies (1 from the 2004 parameter and a later study) demonstrated that ACTH is more effective than VGB for short-term treatment of children with infantile spasms (excluding those with TSC). A small Class III study and a Class IV study found no difference in short-term outcome between ACTH and VGB.

Recommendation. ACTH (Level B) or VGB (Level C) may be offered for short-term treatment of infantile spasms. Evidence suggests that ACTH may be offered over VGB (Level C).

Other agents. *What other agents are as effective as ACTH for treatment of infantile spasms (table e-4)?*

Previously reviewed and updated evidence. All previous and current studies were rated Class IV for treatment using valproic acid (VPA),^{30,31} nitrazepam (NZP),^{32,33} pyridoxine (vitamin B6),^{34,35} zonisamide (ZNS),^{36,37} IVIg,³⁸ thyrotropin-releasing hormone (TRH),³⁹ topiramate (TPM),^{40,e1} levetiracetam (LEV),^{e2} the ketogenic diet,^{e3,e4} and combination therapies using ACTH and VGB,^{e5} hydrocortisone, and VPA.^{e6}

Sulthiame. One Class II randomized, double-blind, placebo-controlled study demonstrated a 30% responder rate to sulthiame vs placebo ($p = 0.025$)^{e7}; this finding is not different from spontaneous remission rates at as early as 1 month from spasms onset as described in limited natural history studies.^{4,5}

ACTH + magnesium sulfate. One Class III randomized, open-label study^{e8} ($n = 38$) comparing combination therapy of ACTH + magnesium sulfate (MgSO_4) with ACTH monotherapy demonstrated better spasms-free outcome (63.2% vs 42.1%, $p = 0.003$) and EEG normalization (47.4% vs 26.3%) for combination therapy at 4 weeks. Mean personal-social developmental quotient using the Gesell test at baseline and after treatment at 24 weeks was significantly improved (from 48.6 to 65.2; $p < 0.05$) for the ACTH + MgSO_4 group and nonsignificant for the control group (ACTH monotherapy).

Conclusions. Data from previously reviewed and updated evidence are insufficient to determine whether VPA, vitamin B6, NZP, LEV, ZNS, TPM, the ketogenic diet, sulthiame, or other novel therapies (e.g., IVIg, TRH) are effective in the treatment of infantile spasms (Class III and IV evidence). A single Class III study showed better outcome for combination therapy with ACTH and MgSO_4 .

Recommendations. The evidence is insufficient to recommend other therapies (VPA, vitamin B6, NZP, LEV, ZNS, TPM, the ketogenic diet, or novel/combination therapies) for treatment of infantile spasms (Level U).

Intermediate to long-term outcomes. *Does successful early treatment of infantile spasms lead to long-term improvement of neurodevelopmental outcomes or decreased incidence of epilepsy (table e-5)?*

Previously reviewed evidence. Seven studies provided Class III and IV evidence for long-term outcome of infantile spasms. None was a randomized or controlled study: 5 were prospective, open-label studies^{17,e6,e9–e11} and 2 were retrospective case series.^{e12,e13} The evidence was insufficient to recommend use of ACTH, corticosteroids, VGB, VPA, and vitamin B6 to improve long-term outcomes of children with infantile spasms. Data also were conflicting or insufficient to conclude that early treatment initiation improves long-term outcomes of children with infantile spasms; 1 prospective Class III study¹⁷ noted an improved neurodevelopmental outcome associated with early therapy commencement of <1 month, whereas another prospective Class III study^{e11} and a retrospective Class IV study^{e13} did not observe such findings.

Updated evidence. Six studies provided Class II, III, and IV evidence for intermediate to long-term outcome of infantile spasms. A Class II large RCT ($n = 107$) reported overall spasms-free outcome in 76% of

the VGB treatment arm vs in 75% of the hormonal therapy arm (synthetic ACTH or prednisolone) at 14-month follow-up.²⁸ Mean Vineland Adaptive Behavioral Scale (VABS) scores did not differ significantly overall between treatment groups (hormonal therapy 78.6 vs VGB 77.5). However, in patients with cryptogenic infantile spasms, the mean score was higher for the hormonal treatment than for the VGB treatment (88.2 vs 78.9, respectively; $p = 0.025$, 95% CI 1.2–17.3). No significant differences in seizure freedom were seen between treatment arms (62% VGB vs 51% hormonal therapy). Outcome of the same 77 patients was described at 4 years using the VABS and an epilepsy questionnaire.^{e14} Assessors were blinded to treatment, providing Class II evidence. There was no significant difference between patients treated with either hormonal therapy or VGB in development and epilepsy outcomes, but patients with cryptogenic infantile spasms who were allocated hormonal treatment had higher mean VABS scores of 96 relative to scores of 63 for those allocated VGB ($p = 0.033$, 95% CI 1–42). Multiple regression analysis was used to examine effects of lead time, age at spasms onset, etiology, and treatment allocation on the developmental outcome at 4 years in the same 77 patients.^{e15} Lead time duration was defined as the time from spasms onset to start of treatment. A 3.9-point decrease in mean VABS was observed for each increase in category of lead-time duration ($p = 0.03$, 95% CI -7.3 to -0.4) after controlling for the effects of treatment and etiology (table e-5). For each month increase in age of spasms onset an increase in developmental quotient of 3.1 points ($p = 0.014$, 95% CI 0.64–5.5) was observed.

One Class III study²⁹ using either natural ACTH or VGB showed better cognitive outcomes in the cryptogenic group, with 40% showing normal development, 40% mild delay, and 20% significant delay. None of the patients in the symptomatic group had normal development posttreatment. No correlation was found between treatment lag time and cognitive outcome.

Conclusions. A Class II study showed that hormonal therapy (ACTH or prednisolone) relative to VGB therapy leads to better neurodevelopmental outcome in children with cryptogenic spasms. One previous Class III study and 1 newer Class II study showed that shorter lag time to treatment improves long-term cognitive outcomes.

Recommendations.

1. Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to VGB in infants with cryptogenic infantile spasms, to possibly improve developmental outcome (Level C).
2. A shorter lag time to treatment of infantile spasms with either hormonal therapy or VGB may be

considered to improve long-term cognitive outcomes (Level C).

CLINICAL CONTEXT This update focuses on questions for which data were insufficient to answer in the 2004 practice parameter. There was a marked paucity of randomized treatment trials carefully designed to provide a definitive answer to any of the questions proposed initially.

The United Kingdom Infantile Spasms Study (UKISS) showed higher responder rates for infants treated with high-dose ACTH and prednisolone than with VGB (Class III); however, the evidence is still insufficient to conclude that prednisolone is as effective as ACTH, because UKISS was underpowered to answer this question.

The current literature suggests that the underlying etiology of infantile spasms is an important outcome determinant. Analysis of children with cryptogenic spasms may provide more insight into a treatment's efficacy by removing the confounding effect of etiology. Class II data from UKISS^{e14} suggest that hormonal agents (e.g., ACTH, prednisolone) are associated with better developmental outcome than VGB. Questions remain, however, regarding optimal ACTH formulation, dose, and treatment duration.

ACTH imposes a burden of treatment because of its cost and mode of administration (IM). Cost can be prohibitive, particularly in the United States. Factors affecting cost are varied and complex and include differing formulations (United States vs elsewhere) and dosing regimens, which can vary by patient age and treatment duration. For a list of online resources regarding drug costs, see appendix e-6. ACTH therapy is usually initiated in a hospital-based setting and usually with nursing supervision. The AEs of hormonal therapy have been extensively discussed in the previous parameter, the most common being hypertension (0%–37%), irritability (37%–100%), infection (14%), and cerebral atrophy (62%)⁶ (see tables e-1–e-3).

VGB has been used in Europe since the late 1980s and in Canada since 1994. In August 2009, the US FDA approved VGB for use in infantile spasms and as add-on therapy for refractory seizures,⁹ with a black box warning for potential permanent visual impairment; the drug is available only through the Lundbeck Inc. restricted Support, Help and Resources for Epilepsy (SHARE) program. Although concerns persist regarding visual field constriction and retinal toxicity with VGB use, the risk appears to be lower with short-term use. In a study of 92 adult patients taking VGB,^{e19} the cumulative VGB dose contributed significantly ($p < 0.001$) to the extent of visual field loss. Another study of 91 children^{e20} us-

ing perimetry showed patients with visual field constriction had received a higher total dose and longer duration of VGB therapy. Electroretinogram (ERG) 30-Hz flicker amplitude has proven to be a useful tool in predicting retinal toxicity in infants treated with VGB^{e21,e22}; however, VGB may not be solely responsible for ERG changes in children with infantile spasms treated with VGB because pretreatment baseline retinal electrophysiology may be abnormal in infantile spasms,^{e23,e24} and the risk may be higher in patients taking VGB with other AEDs.^{e25}

There are also recent reports of abnormal MRI signal intensity or restricted diffusion-weighted imaging affecting the thalamus, basal ganglia, dentate nucleus, and brainstem in patients receiving VGB for infantile spasms.^{e26,e27} However, these changes are reversible when therapy is discontinued, and the clinical significance of the MRI abnormalities is currently unknown.

To date, the evidence is insufficient to support the use of agents other than ACTH and VGB.

FUTURE RESEARCH Multicenter RCTs of infantile spasms with multiple treatment arms (ACTH vs VGB vs prednisolone, or combination hormonal therapy and VGB) are needed to determine the most effective therapy for infantile spasms and should include EEG, clinical seizure occurrence, and standardized developmental outcome measures. The International Collaborative Infantile Spasms Study (ICISS, ISRCTN54363174), a multicenter RCT comparing hormonal therapy + VGB with hormonal therapy alone, is currently underway. It is hoped that this study, and the recently concluded Canadian randomized, double-blind trial of add-on flunarizine to prevent cognitive deterioration associated with infantile spasms (ISRCTN36757519), will provide further evidence regarding the use of combination therapy. In addition, further studies are needed to determine the optimal duration of VGB therapy, to minimize the retinal toxicity AE in patients with infantile spasms.

AUTHOR CONTRIBUTIONS

Cristina Y. Go: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Mark T. Mackay: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Shelly K. Weiss: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Derek Stephens: drafting/revising the manuscript, analysis or interpretation of data, statistical analysis. Thomasin Adams-Webber: study concept or design, acquisition of data. Stephen Ashwal: drafting/revising the manuscript, study concept or design, study supervision. O. Carter Snead: drafting/revising the manuscript, study concept or design, study supervision.

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DISCLAIMER

This statement is provided as an educational service of the American Academy of Neurology and the Child Neurology Society. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN and CNS recognize that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

CONFLICT OF INTEREST

The American Academy of Neurology and Child Neurology Society are committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN and CNS keep separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN and CNS limit the participation of authors with substantial conflicts of interest. The AAN and CNS forbid commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least 3 AAN committees, a network of neurologists, *Neurology*[®] peer reviewers and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

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