AAN Summary of Evidence-based Guideline for CLINICIANS

UPDATE: MEDICAL TREATMENT OF INFANTILE SPASMS

This is a summary of the American Academy of Neurology (AAN) and Child Neurology Society (CNS) guideline update regarding medical treatment of infantile spasms in children.

Please refer to the full 2004 guideline and 2012 update at *www.aan.com* for more information, including definitions of the classifications of evidence and recommendations.

DRUG WARNING

The following treatment has an associated US Food and Drug Administration (FDA) black-box warning:

Vigabatrin (Sabril): *www.accessdata.fda.gov/drugsatfda_docs/label/2011/020427s002lbl.pdf*

Are other forms of corticosteroids as effective as adrenocorticotropic hormone (ACTH) for short-term treatment of infantile spasms?	
Insufficient evidence	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**).

Are low-dose ACTH regimens effective for short-term treatment of infantile spasms?	
Moderate evidence	Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms (**Level B**).

Is ACTH more effective than vigabatrin (VGB) for short-term treatment of infantile spasms?	
Moderate evidence	ACTH may be offered for short-term treatment of infantile spasms (**Level B**).
Weak evidence	VGB may be offered for short-term treatment of infantile spasms (**Level C**).
	Evidence suggests that ACTH may be offered over VGB (**Level C**).

Is there a role for the ketogenic diet or for antiepileptic drugs (AEDs) other than VGB in managing infantile spasms?	
Insufficient evidence	The evidence is insufficient to recommend other therapies (valproic acid, vitamin B6, nitrazepam, levetiracetam, zonisamide, topiramate, the ketogenic diet, or novel/combination therapies) for treatment of infantile spasms (**Level U**).

Does the successful short-term treatment of infantile spasms lead to long-term improvement of neurodevelopmental outcomes or a decreased epilepsy incidence?	
Weak evidence	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**).
	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**).

NOTE

The 2004 AAN and CNS practice parameter on the medical treatment of infantile spasms concluded that ACTH is probably effective (**Level B**) and VGB is possibly effective (**Level C**) for short-term treatment of infantile spasms. It also concluded that VGB is possibly effective for the treatment of infantile spasms in children with tuberous sclerosis (**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 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 (intramuscular). Cost can be prohibitive, particularly in the United States. Factors affecting cost are varied and complex and include differing formulations (United States versus 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 of the published guideline. ACTH therapy is usually initiated in a hospital-based setting and usually with nursing supervision. The adverse effects (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%) (see tables e1–e3 in the published guideline).

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, 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, the cumulative VGB dose contributed significantly ($p<0.001$) to the extent of visual field loss. Another study of 91 children using perimetry showed patients with visual field constriction had received a higher total dose and longer duration of VGB therapy. ERG 30-Hz flicker amplitude has proven to be a useful tool in predicting retinal toxicity in infants treated with VGB; 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, and the risk may be higher in patients taking VGB with other AEDs.

There are also recent reports of abnormal MRI signal intensity and/or restricted diffusion-weighted imaging affecting the thalamus, basal ganglia, dentate nucleus, and brainstem in patients receiving VGB for infantile spasms. 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.

CHILD NEUROLOGY SOCIETY

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