# Response to vigabatrin as first-line treatment for epileptic spasms, not due to TSC


**Keionna M. Brown, RN, MSN, CPNP AC/CP, Jun T. Park, MD**

Epilepsy Center, Neurological Institute, University Hospitals, Case Western University School of Medicine, Cleveland, Ohio, USA


## Introduction

West Syndrome is an infantile epileptic encephalopathy, which typically occurs within the first 2 years of life, with an incidence of 2 to 5 per 10,000 live births.

Epileptic spasms (ES) is the seizure type frequently associated with West Syndrome and is a part of the triad of clinical manifestations including developmental plateau or regression, and an abnormal electroencephalogram (EEG) consistent with hypsarrhythmia.

Standard FDA approved therapies include intramuscular administered adrenocorticotropic hormone (ACTH), oral corticosteroids (OCS), and vigabatrin (VGB), although other non-standard therapies have been used.

Prior literature comparing ACTH, OCS, and VGB still show little agreement regarding best initial therapy, preferred dose, route of administration, and adjunctive therapies.

Our Epileptic Spasms Program at University Hospital Rainbow Babies and Children's Hospital (RBCH) utilizes VGB as first-line therapy for all new cases of ES.

## Objective

Prior literature comparing ACTH, OCS, and VGB still show little agreement regarding best initial therapy, preferred dose, route of administration, and adjunctive therapies. One large multi-center prospective study enrolled 230 participants and compared the three above standard therapies. Their conclusion showed that ACTH was superior and more effective than VGB (55% vs 36%) for children with ES regardless of etiology or development.[1]

Other studies have reported similar lower VGB response rates such as 30% as first-line[2]; another study showed 39.4% VGB response rate.[3] A review of the literature found ACTH to be more effective than VGB for short term treatment of children with ES (excluding those with tuberous sclerosis complex).[4]

Our study analyzed a group of cohorts who received VGB as first-line therapy with a goal to assess therapeutic outcomes. Our hypothesis is that VGB is as effective as ACTH as first-line therapy for ES outside of Tuberous Sclerosis Complex (TSC).
This retrospective study reviewed the RBCH experience with a VGB in-house pharmacy program to assess efficacy of VGB as a first-line treatment for ES independent of etiologies.

## Methods

We performed a single-center, retrospective analysis of all newly diagnosed cases of ES between January 2014 and June 2020 (n=31).

Duration of follow-up was up to 1 year from treatment initiation. Various clinical variables were collected, such as gender (16 male, 15 female), age at onset of diagnosis (range 2 - 36 months; median age 8.8 months), gestational age (range 24 - 41 weeks; median 36 weeks), ethnicity, presence of seizures prior to ES, presence of anti-epileptic drugs (AEDs) prior to ES, developmental assessment (based on Neurologist's assessment and diagnosis of normal, abnormal), etiology (structural (innate vs acquired), genetic/metabolic, cryptogenic, unknown), length of VGB treatment (range 3 - 60 months; median 16.7 months), and visual field (VF) complications **(Table 1).**

Monitoring of vision including assessment of visual acuity and VF was completed within 4 weeks of treatment initiation and every 3-4 months while on therapy, with electroretinogram (ERG) at least once during duration of VGB treatment under anesthesia, and about 3-6 months after discontinuation of therapy. It is challenging to perform conventional VF testing in infants and children, thus the ERG provides a sensitive measure to evaluate for potential early warning signs of retinal toxicity.

This study was approved by the UH Rainbow Babies and Children's Internal Review Board.

**Figure 1: Comparison between responders and non-responders**

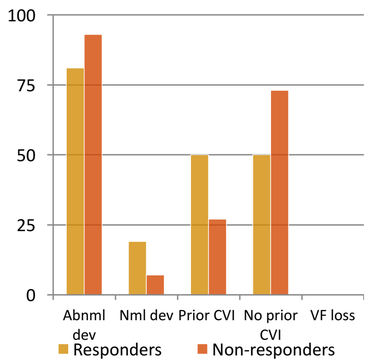



**Table 1: Clinical variables**

| Variable | Entire Cohort (N=31) | VGB Responders (N=16, 52%) | VGB Non-responders (N=15, 48%) |
|---|---|---|---|
| **Sex, N (%)** | | | |
| Female | 15 (48%) | 9 (56%) | 6 (40%) |
| Male | 16 (52%) | 7 (44%) | 9 (60%) |
| **Ethnicity, N (%)** | | | |
| Black | 6 (19%) | 5 (31%) | 1 (7%) |
| White | 17 (55%) | 8 (50%) | 9 (60%) |
| Asian | 2 (7%) | 1 (6%) | 1 (7%) |
| Hispanic | 6 (19%) | 2 (13%) | 4 (26%) |
| **Gestational age (wks) median (range)** | 36 (24-41) | 37 (24-41) | 37.5 (32-40) |
| **Age at diagnosis (mos), median (range)** | 8.8 (2-36) | 8.1 (5-36) | 9.9 (2-36) |
| **Etiology, N (%)** | | | |
| Structural (acq) | 13 (42%) | 8 (50%) | 5 (33%) |
| Structural (innate) | 2 (7%) | 0 | 2 (13%) |
| Genetic/Metabolic | 9 (29%) | 2 (13%) | 7 (47%) |
| Cryptogenic | 6 (19%) | 5 (31%) | 1 (7%) |
| Idiopathic | 1 (3%) | 1 (6%) | 0 |
| **Development at diagnosis, N (%)** | | | |
| Abnormal | 27 (87%) | 13 (81%) | 14 (93%) |
| Normal | 4 (13%) | 3 (19%) | 1 (7%) |
| **Seizures before ES, N (%)** | | | |
| Yes | | | |
| No | 18 (58%) | 9 (56%) | 9 (60%) |
| | 13 (42%) | 7 (44%) | 6 (40%) |
| **Presence of AEDs before ES, N (%)** | | | |
| Yes | 18 (58%) | 9 (56%) | 9 (60%) |
| No | 13 (42%) | 7 (44%) | 6 (40%) |
| **Presence of AEDs post VGB wean, N (%)** | | | |
| Zero | | 4 (25%) | 0 |
| One | | 8 (50%) | 2 (13%) |
| Two | | 2 (12.5%) | 2 (13%) |
| Three | | 2 (12.5%) | 5 (33%) |
| Four | | 0 | 3 (20%) |
| Five | | 0 | 3 (20) |
| **Length of VGB treatment (mos), median (range)** | 16.7 (3-60) | 17.9 (1-60) | 14.9 (2-48) |
| **VF complications, N (%)** | | | |
| Prior CVI | | | |
| No prior CVI | 19 (61%) | 8 (50%) | 4 (27%) |
| VF loss | 12 (39%) | 8 (50%) | 11 (73%) |
| | 0 | 0 | 0 |
| **Hypsarrhythmia on video EEG at diagnosis, N (%)** | | 8 (50%) *Of these, only 1 had this continued pattern but with resolution of ES at 3 months | 9 (60%) |

**Abbreviations:**
**VGB: vigabatrin; ES: epileptic spasms; AEDs: anti-epileptic drugs; VF: visual field; Acq: acquired**

## Results

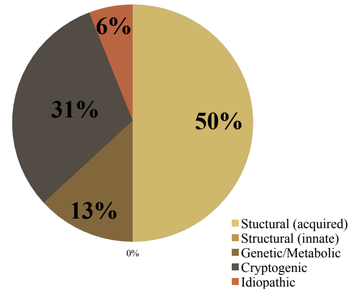
Thirty-one patients followed at RBCH were treated with VGB between January 2014 - June 2020. None of the patients were excluded due to incomplete data.

Sixteen of the 31 infants (52%) with ES were either early responders (clinical and EEG confirmation of spasm-freedom at 2 weeks) or late responders (clinical and EEG confirmation of spasm-freedom after 2 weeks). There were 10 early and 6 late responders. All remained in remission at 12 months. Of the responders, 14/16 (87.5%) demonstrated no worsening of their development; some demonstrated rapid, while others demonstrated slower developmental gains **(Figure 1).**

All 31 infants (100%) experienced no VF deficits related to VGB usage at all 3-4 month interval ophthalmology follow-ups. Three out of seven patients who are still currently taking VGB had prior cortical vision impairment (CVI) but showed no worsening of vision or signs of retinal toxicity **(Figure 1).**

Post-VGB, the early responders were on less AEDs (1-2), compared to the late responders who were taking (1-5) AEDs. Of the responders, 7/16 are currently taking VGB, while the remaining 9/16 have been weaned off of VGB (median length of therapy 10.1 months). There was no significant difference in maximum dosage between the early and late responders (early responder dose range 105-160mg/kg/day vs late responder dose range 50-155mg/kg/day).

**Figure 2: ES etiology for responders**




The non-responder and relapse groups consisted of 15/31 (48%). Amongst the responders, 8/16 had acquired structural etiologies, while 5/16 were cryptogenic.
Amongst the non-responders and patients who relapsed, 5/15 had acquired structural etiologies, while 7/15 had genetic/metabolic etiologies **(Figure 2).**

## Conclusion

VGB appears to be as effective as ACTH as first-line therapy for ES across various etiologies. Our percentage of responders was higher (51.6% vs 36%) than what was reported by Knupp, KG et al. (2016). Few studies have reported similar response rates as ours. One study in particular reported a 56% ES response rate with VGB therapy alone in children with TSC and other etiologies.[3]

Our study had one patient who had a TSC1 paternally inherited heterozygous variant of unknown significance, thus was classified as cryptogenic. There were no pathogenic TSC etiologies in this study.

The potential serious side effect of visual field deficit was demonstrated to not be a concern in the infants in this study for duration of therapy and beyond. Our study confirms that utilizing VGB as first-line therapy compared to other FDA approved treatments (e.g. ACTH or prednisolone) is just as effective with less potential of side effects.

The small sample size of our study was a limitation, although the results confirm previous reports of the efficacy and safety profile of VGB in patients with ES secondary to all etiologies, not just TSC.

## References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3. Camposano SE, Major P, Halpern E, Thiele EA. Vigabatrin in the treatment pf childhood epilepsy: A retrospective chart review of efficacy and safety profile. *Epilepsia.* 2008; 49(7):1186-1191.
4.Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: medical treatment of infantile spasms. Report of the Guideline Development Subcommittee of the American Academy of Neurology and Practice Committee of the Child Neurology Society. *Neurology.* 2012: 78:1974-1980.



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