Archives of Epilepsy

Review

Efficacy of Vigabatrin Oral Suspension in Infantile Epileptic Spasms Syndrome: A Systematic Review

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Cite this article as: Singh VK, Jain R, Rajbhadhandari R, Tyagi V. Efficacy of vigabatrin oral suspension in infantile epileptic spasms syndrome: a systematic review. *Arch Epilepsy*. 2026;32(1):1-8.

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Received: 30.12.2024 **Accepted:** 16.04.2025 **Epub:** 12.01.2026 **Publication Date:** 09.02.2026

DOI: 10.4274/ArchEpilepsy.2025.24168

Infantile epileptic spasms syndrome is a rare and severe epilepsy syndrome in infants. It is identified by clusters of spasms, developmental regression, and hypsarrhythmia. Although there are many different therapeutic options that include the use of vigabatrin (VGB) along with hormonal treatments, the best approach has still not reached a consensus. In this regard, a systematic review of oral suspension VGB is warranted to evaluate efficacy, safety, and its effects on different subpopulations of patients. A systematic review was conducted in accordance with the PRISMA 2020 guidelines (Oxford, UK). Randomized controlled trials, cohort studies, and retrospective analyses conducted in children aged 2 months to 2 years with infantile spasms were selected. Data on spasm cessation, electroencephalography (EEG) normalization, adverse events, and other treatment-specific outcomes were extracted. Bias was assessed through ROBINS-I tool (Cochrane, UK) and Cochrane RoB 2.0 tool (Cochrane, UK). Six studies (34 to 377 participants) from 1999 to 2022 were included. Mean age ranged between 5 and 13.5 months, and male predominance was present. Spasm cessation rates with VGB monotherapy were between 11% and 78%, whereas hormonal therapies reached up to 75%. The response rates for combination therapies that included VGB with hormones stood at 71.5%. The EEG normalization achieved the highest rate of 75% with cosyntropin monotherapy. The VGB had lower rates. Adverse event rates ranged from 0% to 86%, and adverse severe events, including visual field defects, occurred in as many as 19% of participants. Hormonal therapies were associated with irritability and weight gain, and some adverse effects that seemed mitigated by combination therapy. Hormonal therapies were not found to be noticeably better than VGB monotherapy, but combination therapies added better outcomes while maintaining balance between efficacy and safety. Tailored treatment strategy is critical, and further research is required.

Keywords: Infantile epileptic spasms syndrome, vigabatrin, hypsarrhythmia, combination therapy, hormonal treatments, spasm cessation, EEG normalization, adverse events

INTRODUCTION

Infantile epileptic spasms syndrome (IESS), previously referred to as infantile spasms (IS) or West syndrome, represents a severe developmental and epileptic encephalopathy of infancy. This syndrome is characterized by clusters of epileptic spasms, a chaotic interictal electroencephalography (EEG) pattern often described as hypsarrhythmia, and developmental arrest or regression.[1] The incidence is estimated at 0.25 to 0.6 per 1,000 live births, with onset typically within the first year of life, peaking around 4 to 7 months.[2]

IESS is associated with poor neurodevelopmental outcomes when left untreated, often leading to intellectual disability, refractory epilepsy, and severe developmental impairments. Etiologies are diverse, encompassing structural, genetic, metabolic, and acquired causes. Accurate classification by both electroclinical features and etiology is central to diagnosis and management, as emphasized by the International League Against Epilepsy classification system.[3,4]

IESS is resistant to conventional antiseizure drugs and presents some significant challenges in management. The treatment landscape remains very hormonal, dominated by either adrenocorticotropic hormone (ACTH) or oral corticosteroids, and the gamma-aminobutyric acid (GABA)-modulating agent vigabatrin (VGB).[5] Though hormonal therapies are generally considered the first-line treatments for asymptomatic IESS, VGB has become the treatment of choice in IS related to tuberous sclerosis complex (TSC). VGB exerts its effects by

inhibiting GABA transaminase, which increases the levels of the inhibitory neurotransmitter GABA in the brain.[6] This mechanism is especially effective in countering spasms, particularly in etiologies with structural anomalies or TSC.[7]

The introduction of VGB in the 1990s represents a landmark advance in the management of IESS. Its effectiveness has been shown to be effective in both monotherapy and adjunctive therapy. Investigations have shown that VGB results in a spasm cessation rate ranging from 50% to 70%, particularly in the first weeks of treatment.[8-10] Though highly clinically useful, the drug's long-term safety profile still raises concerns, including retinal toxicity and the risk of visual field defects, such that this drug's risk-benefit ratio remains under continued study.[10-12] Furthermore, questions abound about optimal dosing, the duration of therapy, and relative efficacy against other treatments at diverse etiological subgroups.

Despite the many decades of research, the choice of first-line therapy for IS continues to be contentious, as preferences for treatment are very often based on etiology, experience, and available healthcare resources. Most of the past studies have been primarily interested in short-term outcomes such as spasm cessation and EEG normalization, while giving little importance to long-term neurodevelopmental and seizure-free outcomes. Additionally, heterogeneity in study designs, patients studied, and outcome measures has made the synthesis of generalizable and robust conclusions problematic. Based on the evident gaps, this systematic review focuses on the effectiveness of oral VGB suspension for the treatment of IS and aims to present a comprehensive assessment of the therapeutic outcomes, safety profile, and role of VGB in the management of IESS.

MAIN POINTS

- **Treatment efficacy varies by therapy type and subpopulation**
  - Vigabatrin (VGB) monotherapy showed a wide range of spasm cessation rates, from 11% to 78% in the included studies.
  - Hormonal therapies (like cosyntropin or corticosteroids) demonstrated high cessation rates, reaching up to 75% , and were associated with the highest rates of electroencephalography normalization (75% with cosyntropin monotherapy).
  - Combination therapy (VGB with hormones) was found to have better response rates, reaching 71.5%, and may offer a better balance between efficacy and safety.
  - Etiology is critical: VGB is the treatment of choice and particularly effective for infantile spasms (IS) associated with tuberous sclerosis complex, often exceeding the response of hormonal therapy in this subgroup.
- **Safety profile highlights the risk of visual defects with VGB**
  - Adverse event rates ranged broadly from 0% in tightly controlled settings to 86% in broader clinical applications.
  - VGB is primarily associated with side effects such as lethargy, drowsiness, and the severe adverse event of visual field defects (in as many as 19% of cases in the abstract).
  - Hormonal therapies are mainly associated with irritability and weight gain.
  - Combination therapies may mitigate some risks, but visual field toxicity remains a concern for VGB.
- **A tailored treatment strategy is recommended**
  - The review concludes that hormonal therapies were not found to be noticeably better than VGB monotherapy overall, but combination therapies added better outcomes.
  - The optimal choice of first-line therapy for IS remains contentious and should be an individualized, tailored treatment strategy based on the patient's underlying etiology, safety considerations, and response to therapy.
  - Given the findings, the recommendation is to consider hormonal therapies first-line, but VGB-inclusive combination therapy is a viable alternative if hormonal treatments are ineffective or contraindicated.

METHODS

Inclusion and Exclusion Criteria

Studies were included if they: (1) involved patients aged between 2 months and 2 years with IS, (2) evaluated the efficacy of VGB, either as monotherapy or in combination with other drugs, (3) were designed to have measurable endpoints such as cessation of spasms, EEG normalization, or adverse events (4) were either randomized controlled trials (RCTs), cohort studies, or case-control studies, and (5) were published in a peer-reviewed journal in the English language. The exclusion criteria were for studies that addressed any of the following areas: (1) where VGB had not been evaluated per se, (2) conducted on patients with disorders apart from IESS, (3) lacked quantitative data on efficacy or safety, (4) were a review article, editorial or letter without original data or sources, or (5) duplicated data or overlapped patient cohorts.

Review Design

The PECOS framework was created in compliance with the reporting guidelines of PRISMA 2020 (University of Oxford, UK; University of Sydney, Australia)[13] to ensure systematic identification and evaluation of relevant studies. The population (P) consists of children between the ages of 2 months and 2 years, diagnosed with IS. The exposure (E) was oral VGB suspension administration. The comparator (C) includes other therapies like ACTH, corticosteroids, or placebo. The outcomes (O) were spasm cessation, EEG normalization, and adverse event rates. The study design (S) included RCTs, cohort studies, and case-control studies.

Database Search Protocol

The comprehensive search strategy was implemented on six databases: PubMed, Embase, Cochrane Library, Scopus, Web of Science, and ClinicalTrials.gov. An exact and sensitive search was carried out using Boolean operators and MeSH keywords. Terms related to "infantile spasms", "VGB", "oral suspension", "treatment outcomes", and "adverse events" were used in the search (Table 1). Variations of the keywords and synonyms were considered to capture all relevant literature. Filters for age group, study design, and language were applied where appropriate.

Data Extraction Protocol

Data were extracted with a standardised protocol to make it uniform and accurate. The extracted items include the following: title of the study, names of authors, year of publication, design of study, sample size, number of patients, including age, gender, and comorbid conditions, information on the intervention, including dosage of VGB, treatment duration, comparison treatments, and outcome measures, which include spasm resolution, EEG return to normal, side effects, and a statistical summary that includes confidence

Table 1. Search strings utilised across the assessed databases

Database	Search string
PubMed	("infantile epileptic spasms syndrome"[MeSH] or "West Syndrome") and ("vigabatrin"[MeSH] of "gamma-aminobutyric acid transaminase inhibitor") and ("oral suspension" or "administration and dosage") and ("treatment outcomes").
Embase	("infantile epileptic spasms syndrome"/exp or "West syndrome") and ("vigabatrin"/exp or "gaba transaminase inhibitor") and ("oral suspension" or "dose regimen") and ("efficacy" or "safety").
Cochrane Library	("infantile epileptic spasms syndrome" or "West syndrome") and ("vigabatrin" or "gamma-aminobutyric acid transaminase inhibitor") and ("oral suspension") and ("randomized controlled trial" or "observational study").
Scopus	TITLE-ABS-KEY ("infantile epileptic spasms syndrome" or "West syndrome") and TITLE-ABS-KEY ("vigabatrin") and TITLE-ABS-KEY ("oral suspension") and TITLE-ABS-KEY ("spasm cessation" or "EEG normalization").
Web of Science	("infantile epileptic spasms syndrome" or "West syndrome") and ("vigabatrin" or "gamma-aminobutyric acid transaminase inhibitor") and ("oral suspension") and ("efficacy" or "adverse events").
ClinicalTrials.gov	("infantile epileptic spasms syndrome" and "vigabatrin" and "oral suspension" and "adverse events") and (phase 2 or phase 3).

EEG: Electroencephalography, MeSH: Medical Subject Headings

intervals (CI) and p-values. Two reviewers independently extracted the data, and any discrepancy was resolved by discussion or referral to a third reviewer. This approach reduced the error, increasing the reliability of the extracted data.

Risk of Bias Protocol

Risk of bias was assessed for included studies in the ROBINS-I tool (Cochrane, UK)[14] for non-randomized studies and the RoB 2.0 tool (Cochrane, UK)[15] for RCTs. ROBINS-I (Cochrane, UK) domains included confounding, selection of participants, classification of interventions, and outcome measurement. RoB 2.0 (Cochrane, UK) evaluated the process of randomization, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selective reporting. Every domain was rated low, moderate, serious, or a critical risk of bias.

RESULTS

A total of 374 records were identified from the database search, and no records were obtained from the registers (Figure 1). After the removal of 43 duplicate entries, 331 records were screened for relevance. No records were excluded in the initial screening phase. Of these, 331 full-text reports were sought, of which 34 could not be retrieved. Thereafter, 297 full-text reports were assessed for eligibility. Of these, 291 reports were excluded on the grounds that 62 failed to satisfy the PECOS criteria, 74 were literature reviews, 58 concentrated on adult populations, 48 were case reports, and 49 were editorials. Finally, six studies[16-21] were included in the systematic review, and there were no further reports of newly included studies.

Geographic Distribution and Temporal Context

The studies included in this review were conducted in different regions and time periods, highlighting the global efforts to investigate the treatment of IS (Table 2). Research was conducted in the United Kingdom (UK)/Netherlands,[16] Australia,[17] Pakistan,[18] the USA,[19] and multinational collaborations across the UK, Australia, Germany, and Switzerland.[21] The studies ranged in publication years from 1999[16] to 2022[17,19] reflecting evolving approaches and advancements in the understanding of IS treatment.

Study Designs and Sample Sizes

Most studies were RCTs, consisting of controlled comparisons between VGB and other treatments.[16,19-21] Two were retrospective,

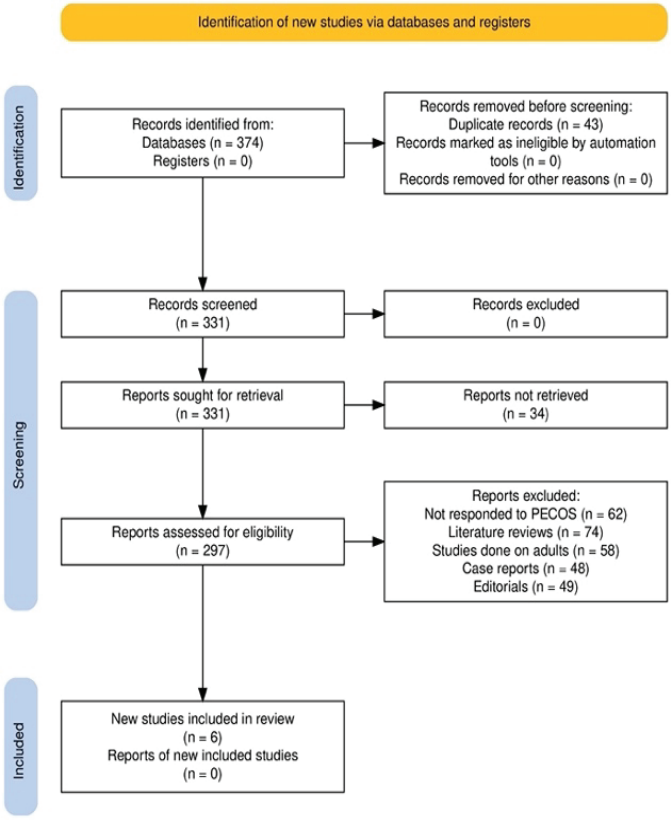

Figure 1. PRISMA study selection process for this review

based on real-world data from clinical records.[17,18] Sample sizes were highly variable, from 34 participants[19] to 377[21] with smaller studies made detailed therapeutic observations possible, while larger studies allow for greater generalisability.

Participant Characteristics

The mean age at spasm onset ranged considerably, and thus the populations involved were heterogeneous. The lowest mean age recorded was 5±1.4 months,[18] while the highest was at 13.5 months, a median value.[16] All the studies demonstrated a predominance of males in their patient demographics. Males represented between 53%.17 to 64.7%[19] of all cases. This trend in patient demographics has been observed to fit previous reports of a slightly higher prevalence of IS in male infants.

Table 2. Demographic variables assessed

Author ID	Year	Location	Study design	Sample size	Mean age (in years)	Male/female ratio	Follow-up period
Appleton et al.[16]	1999	UK/Netherlands	RCT	40	13.5 months (median)	60% male	24 weeks
Dzau et al.[17]	2022	Australia	Retrospective	151	8.2±1.3 months	53% male	42 days
Ibrahim et al.[18]	2010	Pakistan	Retrospective	56	5±1.4 months	62.5% male	6 months
Knupp et al.[19]	2022	USA	RCT	34	6 months (mean)	64.7% male	2 weeks
Lux et al.[20]	2004	UK	RCT	107	6.2±1.5 months	58% male	14 days
O'Callaghan et al.[21]	2017	UK/Australia/ Germany/Switzerland	RCT	377	7±2.3 months	Not reported	42 days

RCT: Randomized controlled trial

Duration of Follow-up

Follow-up durations ranging from a minimum of 2 weeks[19] to as much as 42 days.[17,21] Long-duration follow-ups helped evaluate in greater depth not only treatment efficacy but also side effects, while shorter-duration follow-ups primarily reflected immediate treatment results in the form of cessation of spasms and EEG normalization.

Types of Treatment and Dose Intervals

The studies assessed different treatment modalities: for example, VGB as monotherapy, hormonal treatments like prednisolone or cosyntropin (Table 3). The dosages for VGB varied from 12.5 mg/kg/day[18] to 150 mg/kg/day.[16,17,20,21] The hormonal treatments, such as cosyntropin, have been used at similar dosages across all the studies, which can be useful for comparison.

Response Rates

Spasm cessation rates with VGB monotherapy exhibited a broad range, spanning from 11% in some real-world clinical settings to as high as 78% in controlled trials, suggesting variability in response based on patient characteristics and study design.[16,19] In contrast, hormonal therapies demonstrated cessation rates reaching up to 75%[20] though these rates were not consistently superior to those of VGB across all populations. Notably, in cases of IESS associated with TSC, VGB was reported to be particularly effective, with a response rate exceeding that of hormonal therapy.[21-34] While combination therapy incorporating both VGB and hormonal treatments demonstrated improved response rates, these findings underscore the need to tailor treatment selection based on etiology and individual patient response. This approach avoids assuming the universal superiority of hormonal interventions.[18,21]

EEG Normalization

EEG normalization was another important secondary measure in most of the studies. The highest normalization rates were reported with cosyntropin monotherapy, where 75% of patients had resolution of hypsarrhythmia.[19] Similarly, hormonal therapies had normalization rates of 68% in some populations.[20] On the other hand, VGB monotherapy had lower normalization rates, which is consistent with its relatively lower efficacy in achieving complete spasm control.

Adverse Event Rates

Adverse events were seen within all treatment groups. For example, the rate has ranged from 0% for tightly controlled settings[16] to 86% for a broader clinical application.[19] Severe adverse events were less common: the rates were 12% in those on hormonal therapy and 9% in those who received VGB in one comparison.[17] The comparison of combination therapies with VGB monotherapy revealed relatively lower rates of severe adverse events.[21]

Types of Adverse Events

The adverse events varied depending on the treatment. VGB was mainly associated with lethargy, drowsiness, and visual field defects[18,19,21] while hormonal therapies were mainly associated with irritability and weight gain.[20] Combination therapies mitigated some of these risks, except that visual field toxicity remained an issue for VGB.[21]

Etiology and Subpopulations

The studies targeted diverse IESS subpopulations. Some studies targeted newly diagnosed IESS with classic hypsarrhythmia[16] while others excluded tuberous sclerosis to assess non-TSC IS.[17,20] Such distinctions are critical because the etiology of IESS significantly influences the treatment response. For example, VGB is highly effective in IESS associated with tuberous sclerosis but is less effective in other forms of IESS.[21]

Quality Levels Observed

Among the RCTs, most studies had a low risk of bias in multiple domains (Figure 2). However, there were specific concerns regarding the randomization process (D1) in Appleton et al.[16] and O'Callaghan et al.[21] as well as selective reporting (D3) in Lux et al.[20] Appleton et al.[16] and O'Callaghan et al.[21] also had some concerns about deviations from intended interventions (D4). Altogether, RCTs scored a low risk of bias, which ensures strong methodological quality, although with minor limitations in isolated domains.[16,19-21]

Table 3. Efficacy of VGB observed across the included papers

Author ID	Groups assessed	Vigabatrin dosage (mg/kg/day)	Duration of therapy (weeks)	Response rate (% cessation of spasms)	EEG normalization rate (%)	Adverse event rate (%)	Adverse event type(s)	Concurrent therapies	Study population characteristics (etiology/genotype of IESS)	Conclusion assessed
Appleton et al.[16]	VGB vs. placebo	50-150 mg/kg/day	5 days	78% (95% CI: 55-89%)	Not reported	0%	None reported	None	Newly diagnosed IESS, classic hypsarrhythmia	VGB effective, recommended as first-line
Dzau et al.[17]	PNL40, PNL60, VGB	100-150 mg/kg/day	42 days	PNL60: 63%, VGB: 45% (P=0.01)	EEG normalization: not significant	Severe effects: 12% (PNL), 9% (VGB)	Hospitalization, irritability	Sequential hormone therapy	Non-tuberous sclerosis IESS	Hormone escalation effective in non-responders
Ibrahim et al.[18]	VGB vs. ACTH	12.5-150 mg/kg/day	6 weeks	55.3% (ACTH: 50%)	Partial EEG improvement: 32%	Relapse: ACTH 55%, VGB 33%	Drowsiness, lethargy	ACTH second-line	Symptomatic/ idiopathic IESS	VGB preferred for first-line
Knupp et al.[19]	Cosyntropin, VGB, cosyntropin+VGB	Not specified	2 weeks	Cosyntropin: 75%, VGB: 11%, combination: 38% (p<0.01)	Hypsarrhythmia resolved: 75% (cosyntropin)	Adverse events: 86%, serious: 19%	Special interest: 42% (no significant differences)	None	New-onset IESS with hypsarrhythmia	Cosyntropin more effective than VGB for short-term outcomes
Lux et al.[20]	Hormones vs. VGB	100-150 mg/kg/day	14 days	VGB: 54%, hormones: 73% (p=0.043)	Hypsarrhythmia resolution: 68% (hormones)	Adverse effects: 55% (hormones)	Irritability, weight gain	Prednisolone, tetracosactide	Severe IESS excluding tuberous sclerosis	Hormones superior, recommend short duration
O'Callaghan et al.[21]	Hormones vs. hormones+VGB	100-150 mg/kg/day	42 days	Combination: 71.5%, hormones: 56.5% (p=0.002)	Electro-clinical improvement: 60% (combination)	Adverse effects: 18% (VGB)	Visual field defects	Hormonal therapy+VGB	Severe IESS without tuberous sclerosis	Combination superior, caution in toxicity

VGB: Vigabatrin, PNL: Peripheral nasal limit, ACTH: Adrenocorticotropic hormone, CI: Confidence interval, EEG: Electroencephalography, IESS: Infantile epileptic spasms syndrome

The cohort studies showed more variation in bias levels (Figure 3). The risk of bias for Dzau et al.[17] was low across many domains, but the authors had noted moderate concerns in the classification of interventions (D6). On the other hand, Ibrahim et al.[18] had moderate bias in many key domains such as confounding (D1), selection of participants (D2), and classification of interventions (D3). However, most of the other domains presented with low bias, thereby making the overall risk of bias for this study moderate.[17,18]

DISCUSSION

Mechanism of Action and Therapeutic Profile of VGB

VGB is associated with its antiepileptogenic properties due to an irreversible inhibition of the GABA catabolizing enzyme breakdown called transaminase, thus raising central nervous system inhibitory neurotransmitter GABA levels.[22] Other scientific research has shown that VGB can interfere with the glutamate-glutamine cycle between neurons and the central nervous system astrocyte cells, which contributes to its therapeutic effect in this patient population.[23] Early investigations conducted in 1983 showed that VGB is both an effective and tolerated drug among adult patients diagnosed with refractory epilepsy.[24] In 1989, its application extended to a refractory form of IESS, predominantly as add-on therapy, and proved highly efficacious, especially among TSC cases.[25-27] Several studies over the years assessed VGB's safety and efficacy profile for its use as the IESS treatment.[25-29] However, such studies also brought into view severe adverse effects associated with its use. According to a meta-analysis, VGB was related to retinal toxicity in 29% of the patients [95% confidence interval (CI): 7-69%] visual field defects were noted in 28% of patients (95% CI: 4-78%) and magnetic resonance imaging abnormalities in 21% of patients (95% CI: 15-29%).[30] Despite these risks, the therapeutic efficacy of VGB in IESS remains well established. VGB was approved by the United States Food and Drug Administration in 2009 for use as monotherapy in IESS and as adjunctive therapy for refractory complex partial seizures.[31]

Thematic Findings Across the Review

The included studies showed important patterns and differences in the efficacy and safety of VGB and hormonal therapies in the treatment of IESS, with varying degrees of similarity and divergence among the studies. The conclusions drawn from the studies by Appleton et al.[16] and Ibrahim et al.[18] which show similar results, show indicate that VGB monotherapy can achieve

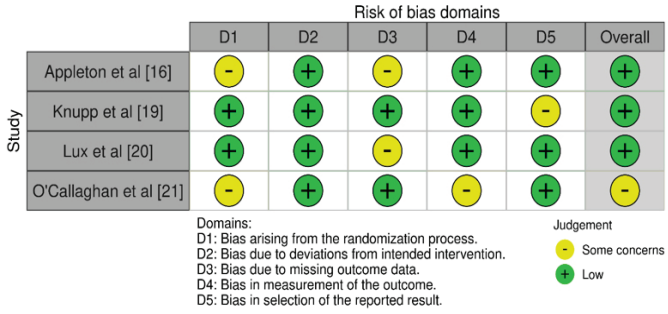

Figure 2. Bias assessed across the RCTs
RCTs: Randomized controlled trials

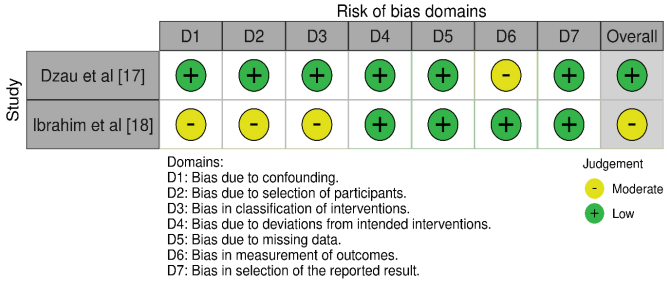

Figure 3. Bias assessed across the cohort studies

medium success as a first-line therapy, especially in newly diagnosed IESS cases. Both studies found a good rate of response to VGB; Appleton et al.[16] found a 78% spasm cessation rate, while the similar study by Ibrahim et al.[18] reported 55.3%, an observation which might be associated with the study population as well as the follow-up time.

The results by Knupp et al.[19] and Lux et al.[20] are quite similar. However, although they differ in the degree of superiority, a cosyntropin response is 75% in the former, while hormonal therapy was 73% in the latter as reported by Lux et al.[20] Both studies highlighted that VGB monotherapy was ineffective in non-TSC-associated IESS, as evidenced by its low response rates of 11% and 54%, respectively.

Dzau et al.[17] and O'Callaghan et al.[21] reported combination therapies. Both studies reported that the effects of combination therapies were better than hormones alone, but the magnitude of effect differed between the two studies. O'Callaghan et al.[21] documented a higher rate of response at 71.5% for combinations as compared to 56.5% for hormone therapy alone, while Dzau et al.[17] mentioned a minimal effect with insignificant differences in the rate of normalization of EEG.

Another area of distinction was adverse event profiles. Appleton et al.[16] had no adverse events, whereas in the study by Knupp et al.[19] 86% of patients experienced adverse events. Safety profiles of combination therapies studied in O'Callaghan et al.[21] were more favorable than the monotherapy with VGB, as reported in Dzau et al.[17] in which severe adverse effects, including hospitalization, occurred in 9% of cases.

Alignment with Previous Reviews

The efficacy of hormonal monotherapy in IESS has been well-documented, particularly in non-TSC-associated cases; however, recent meta-analyses challenge the notion that it is universally superior to VGB.[32,33] While hormonal therapies, including ACTH and corticosteroids, have shown robust response rates, several studies indicate that VGB is at least equally effective and, in some cases, superior, particularly when considering long-term neurodevelopmental outcomes and EEG normalization.[34,35] Additionally, the variability in study designs and patient demographics has contributed to inconsistencies in reported efficacy, making it imperative to interpret these findings with caution. The optimal treatment approach should therefore be individualized, incorporating factors such as etiology, safety considerations, and patient response to therapy.[19,22]

Our results are somewhat different from those of Xu et al.[33] who found no significant difference in spasm cessation rates between hormonal monotherapy and combination therapy (hormones+VGB) in two RCTs. In contrast, our review suggested that combination therapies could improve outcomes in some cases, though this finding requires cautious interpretation due to variability across studies.

Similar to our results, response rates to VGB have been much higher in patients with TSC-associated IESS, as reported by Prezioso et al.[34] The spasm cessation rate of 67% across observational studies and 88% in RCTs, in TSC patients, closely coincides with the higher efficacy of VGB in such a subgroup, as determined in our review. However, both reviews pointed out limitations because of high heterogeneity and low levels of evidence, thus requiring further robust studies to strengthen therapeutic recommendations.

Both our review and the results of Golec et al.[35] pointed out potential safety issues with VGB treatment, especially visual field defects and neuroimaging abnormalities. This only underscores the necessity to closely monitor the long-term safety of VGB. Our review did suggest that combination therapies may reduce some adverse effects, but Golec et al.[35] raised broader safety concerns, which limit the general use of VGB restricting its use only to specific indications like TSC-associated IESS.

Our review provided a world view of IESS management, whereas Sahu et al.[36] highlighted the unique epidemiological and clinical challenges in South Asia. Both analyses commented on an increased male-to-female ratio in IESS presentations, which is consistent with more general epidemiological trends. Additionally, Sahu et al.[36] pointed out other regional barriers: these include the lack of availability of ACTH and VGB, and more resource-specific strategies are of utmost importance, which cannot be the prime focus in our review.

Study Limitations

This study had several limitations due to the variability in study designs, sample sizes, and follow-up durations among the included studies. The heterogeneity among the patients' demographics (such as mean age at spasm onset and male-to-female ratios) may have resulted in confounding factors limiting the generalizability of the findings. Variability in treatment protocols, particularly dosages

and durations of VGB and hormonal therapies, complicated direct comparisons between studies. The inconsistent reporting of secondary outcomes, such as EEG normalization rates and long-term neurodevelopmental outcomes, limited the ability to draw definitive conclusions about the overall efficacy of VGB. Adverse event rates were sometimes reported inconsistently and some did not provide adequate descriptions of the safety profile, which made it challenging to thoroughly assess the risk-benefit ratio of VGB monotherapy or combination therapies.

Recommendations and Clinical Implications

Hormonal therapies should be considered the first-line of treatment for IS, because of their efficacy in spasm cessation and EEG normalization. If hormonal treatments alone prove to be ineffective or are contraindicated, combination therapy with VGB should be considered a viable alternative. Future clinical trials should ensure that all treatment protocols standardize the dosage and duration to allow for more comparisons. Long-term follow-up studies are also required to evaluate the effects of these treatments on neurodevelopmental outcomes and seizure recurrence. Adverse events should be systematically monitored and reported to provide a clearer understanding of the safety profiles of these treatments, particularly the retinal toxicity associated with VGB. Tailored approaches that account for the underlying etiology and patient-specific characteristics should guide clinical decision-making.

CONCLUSION

This review highlights the complexities in selecting optimal therapy for IS, as the comparative efficacy of VGB and hormonal treatments remains dependent on patient-specific factors, particularly etiology. While hormonal therapies have long been considered first-line treatments, recent meta-analyses indicate that VGB exhibits comparable, if not superior, efficacy in certain subgroups, especially in IESS cases linked to TSC. Moreover, EEG normalization and long-term neurodevelopmental outcomes may not always favor hormonal monotherapy over VGB. Combination therapies incorporating both VGB and hormonal agents have demonstrated promising outcomes, though their superiority over individual therapies requires further investigation. Given these findings, treatment decisions should be made on a case-by-case basis, weighing efficacy, safety profiles, and individual patient response rather than assuming a universal advantage of hormonal therapy.

Footnotes

Authorship Contributions

Surgical and Medical Practices: V.K.S., R.R., Concept: V.K.S., Design: V.T., Data Collection or Processing: R.R., Analysis or Interpretation: V.T., Literature Search: R.J., Writing: R.J.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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