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Systematic Review

Safety and Efficacy of Rational Polytherapy with Sodium Valproate and Lamotrigine for Pediatric Drug-Resistant Epilepsy: A Systematic Review and Meta-Analysis

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Abstract

Background: Drug-resistant epilepsy (DRE) affects approximately one-third of individuals with epilepsy, where seizures remain uncontrolled despite appropriate trials of at least two antiseizure medications (ASMs). Neuroinflammation, specifically chronic microglial activation, plays an important role in epileptogenesis, seizure perpetuation, and pharmacoresistance. Traditionally, antiseizure medications (ASMs) target neuronal excitability through modulation of ion channels and neurotransmitter systems; however, several ASMs, including sodium valproate and lamotrigine, have demonstrated anti-inflammatory and microglia-modulating properties beyond their conventional antiseizure mechanisms. Rational polytherapy involving combinations of ASMs with complementary mechanisms and anti-neuroinflammatory effects may provide enhanced seizure control while minimizing adverse effects. Among available combinations, sodium valproate and lamotrigine have consistently been regarded as one of the few combinations demonstrating potential pharmacodynamic synergism. Although several clinical studies have evaluated this combination in pediatric DRE, the overall evidence has not been quantitatively synthesized. **Objectives:** To systematically evaluate the efficacy and safety of rational polytherapy with sodium valproate plus lamotrigine in children with drug-resistant epilepsy. **Methods:** Electronic databases, including PubMed, Medline, Scopus, Embase, Web of Science, Google Scholar, PubMed Central, ScienceDirect, Cochrane Library, and clinicaltrials.gov, were systematically searched. Studies involving pediatric patients aged 18 years or less with DRE receiving polytherapy regimens containing sodium valproate plus lamotrigine were included. Primary outcomes were total treatment effect defined as $\geq$50% seizure reduction and seizure freedom. Secondary outcomes included changes in seizure frequency, adverse events, treatment discontinuation, and serious adverse events. Risk of bias was assessed using the Cochrane Risk of Bias tool and Newcastle–Ottawa Scale. Meta-analyses were performed using random-effects models. **Results:** A total of 7 studies met the eligibility criteria. The pooled proportion of patients achieving an overall treatment response was 65.3% (95% CI 51.8–78.8%), with high heterogeneity (I^2 = 63.4%, p = 0.027). Rational polytherapy with sodium valproate plus lamotrigine combination provided preliminary comparative evidence of higher responder rates in a single comparative trial, requiring confirmation in larger randomized trials. Overall, sodium valproate plus lamotrigine was well tolerated, and most reported adverse events were mild to moderate in severity. The pooled adverse event rate was 18.1% (95% CI 8.3–28.0%), with high heterogeneity (I^2 = 64.3%, p = 0.024). **Conclusions:** Rational polytherapy with sodium valproate plus lamotrigine that have both complementary antiseizure and immunomodulatory mechanisms appears

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to represent an effective and generally well-tolerated therapeutic strategy for pediatric drug-resistant epilepsy. However, the basis of this conclusion is derived mainly from observational studies, requiring confirmation in larger randomized trials. This systematic review provides quantitative evidence supporting its clinical use while highlighting the need for larger prospective comparative studies to strengthen the evidence base.

Keywords: pediatric epilepsy; drug-resistant epilepsy; rational polytherapy; sodium valproate; valproic acid; lamotrigine; antiseizure medications; microglia; neuroinflammation

1. Introduction

Epilepsy is one of the most common chronic neurological disorders, affecting more than 50 million individuals worldwide and contributing substantially to neurological morbidity and mortality. About 80% of epilepsy cases are in middle- and low-income countries where access to medical services is grossly inadequate. Globally, an estimated 2.4 million people are diagnosed with epilepsy annually, and the majority are in resource-limited countries [1]. Nearly half of all new cases of epilepsy occur during childhood and adolescence. Children with epilepsy experience not only recurrent seizures but also substantial cognitive, behavioral, psychosocial, and educational impairments that can persist into adulthood. The International League Against Epilepsy (ILAE) defined epilepsy as a chronic disorder of the brain characterized by an enduring disposition towards recurrent unprovoked seizures. Clinically, diagnosis of epilepsy is made when at least two unprovoked seizures occur more than 24 h apart, or one unprovoked seizure occurs associated with abnormal findings on an EEG or brain imaging scan that indicate a high probability of a second seizure [2]. Approximately 30% of patients continue to experience seizures despite adequate treatment, thereby meeting criteria for drug-resistant epilepsy (DRE) [3]. The ILAE defines DRE as the failure of adequate trials of two tolerated, appropriately chosen, and administered ASM regimens, whether implemented as monotherapies or in combination, to achieve sustained freedom from seizures [3,4].

Children with DRE represent one of the most challenging populations encountered in pediatric neurology. Persistent seizures during critical periods of brain maturation adversely affect neurodevelopment and cognitive function. It also leads to impaired language skills, learning difficulties, and poor psychosocial well-being. These children usually have increased risks of injury, hospitalization, sudden unexpected death in epilepsy (SUDEP), and long-term disability. Although epilepsy surgery, ketogenic dietary therapy, vagus nerve stimulation, and other neuromodulation techniques may provide effective alternatives for carefully selected patients, many children are either unsuitable candidates or lack access to these specialized interventions. Consequently, optimization of pharmacotherapy remains the cornerstone of treatment for a large proportion of pediatric DRE patients [5,6]. The primary therapeutic goal in pediatric epilepsy is complete seizure freedom without unacceptable adverse effects. For most children, this objective can be achieved using appropriately selected ASM monotherapy. However, approximately one-third of pediatric patients continue to experience seizures despite adequate treatment and eventually develop drug-resistant epilepsy (DRE), a condition associated with significantly worse neurological and developmental outcomes [3,6].

Over the past two decades, increasing evidence has established neuroinflammation as a central contributor to epileptogenesis, seizure propagation, and treatment resistance. Both experimental and clinical studies have demonstrated activation of innate immune pathways within epileptic brain tissue, characterized by increased expression of pro-inflammatory

cytokines, chemokines, complement proteins, and damage-associated molecular patterns (DAMPs) [7,8]. Among the cellular mediators of neuroinflammation, microglia have emerged as key regulators of epileptogenesis, network remodeling, and severe pharmacoresistance [9]. Persistent microglial activation may enhance neuronal excitability, disrupt blood–brain barrier integrity, alter synaptic transmission, and facilitate recurrent seizures, thereby creating a self-perpetuating cycle of inflammation and epileptogenesis driving pharmacoresistance [10]. Several ASMs exhibit anti-inflammatory properties independent of their traditional anticonvulsant actions. For example, valproate inhibits histone deacetylases and attenuates inflammatory gene expression in activated microglia, whereas lamotrigine suppresses microglial activation, reduces the production of pro-inflammatory cytokines and attenuates oxidative stress [11]. The concept of rational polytherapy advocates combining ASMs with complementary and ideally synergistic mechanisms of action to maximize efficacy while minimizing toxicity. Traditionally, rational polytherapy has focused on combining agents targeting distinct neuronal pathways. However, emerging evidence suggests that incorporating ASMs with anti-neuroinflammatory and microglia-modulating properties may provide additional therapeutic benefits in DRE by addressing both neuronal and immunological mechanisms underlying seizure generation [12].

Among these combinations, the concurrent administration of sodium valproate (VPA) and lamotrigine (LTG) has emerged as one of the most prominent examples of rational polytherapy. This combination utilizes distinct yet complementary pharmacodynamic properties. Sodium valproate functions as a broad-spectrum agent that enhances gamma-aminobutyric acid (GABA)-mediated inhibitory neurotransmission, attenuates T-type calcium currents, and blocks voltage-gated sodium channels [13]. Lamotrigine, on the other hand, exerts its primary effect by selectively stabilizing presynaptic voltage-gated sodium channel membranes, thereby inhibiting the hyper-synchronous release of excitatory amino acids such as glutamate [14]. When paired, these distinct mechanisms create a powerful pharmacodynamic synergy that can disrupt refractory seizure networks where single agents fail [15]. Beyond pharmacodynamics, this combination triggers a profound pharmacokinetic interaction. Valproate acts as a potent inhibitor of the hepatic enzyme UDP-glucuronosyltransferase (UGT), which is the primary metabolic pathway responsible for lamotrigine clearance. By inhibiting this pathway, valproate can reduce the oral clearance of lamotrigine by roughly 50%, effectively doubling its elimination half-life and substantially boosting circulating plasma levels [15]. While separate clinical trials have documented individual success rates for these medications [16], a unified, quantitative analysis focused explicitly on children with drug-resistant epilepsy remains sparse. Therefore, in this review we aim to qualitatively and quantitatively analyze the available literature to determine the pooled safety and efficacy of rational polytherapy with sodium valproate and lamotrigine in the pediatric DRE population, establishing definitive, evidence-based recommendations for clinical practice.

2. Materials and Methods

2.1. Study Design and Protocol

We conducted a systematic review and meta-analysis of published literature on the safety and efficacy of rational polytherapy with sodium valproate and lamotrigine for pediatric drug-resistant epilepsy. The protocol employed for this study was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The research team prepared the review protocol, which was then reviewed by two experts in the field who were not part of the research team. The review protocol was prepared and registered on PROSPERO (the International Prospective Register of Systematic Reviews)

"Ref-2026: CRD420261438771" and is available online at https://www.crd.york.ac.uk/PROSPERO/view/CRD420261438771 (accessed on 3 July 2026).

2.2. Sources of Data Collection and Search Strategy

Major electronic databases were systematically searched for published data, including PubMed, Medline, Scopus, Embase, Web of Science, Google Scholar, PubMed Central, and ScienceDirect. Two research registries comprising the Cochrane Central Register (Cochrane Library, all issues; www.cochranelibrary.com, accessed on 1 May 2026) and clinicaltrial.gov (www.clinicaltrials.gov, accessed on 15 April 2026) were searched for relevant clinical trials. A search of the reference lists of the included articles for related articles was conducted, and effort was made to search for unpublished studies by contacting experts. The Medical Subject Headings (MeSH) terms, Emtree terms, and regular keyword search strategies were used for the identification of the relevant articles. The MeSH strategy and Emtree terms were mainly used for searching PubMed, Medline, Embase, Scopus, and Web of Science, while both MeSH and regular keywords were employed for searching the other databases.

2.3. Search Content

The combination of the following search terms were used for each database for identification of relevant articles: "valproate", "sodium valproate", "valproic acid", "lamotrigine", "epilepsy", "pediatric", "children", "polytherapy", "rational polytherapy", "combination therapy", "drug resistant epilepsy", "DRE", "effectiveness", and "therapeutic effect".

2.4. Inclusion and Exclusion Criteria

The following inclusion criteria were used: (1) Studies published between 2000 and 2026 focusing on pediatric cohorts aged $\leq$18 years or cohorts containing predominantly pediatric populations (mean/median age $\leq$ 18 years). (2) Both experimental studies (randomized and non-randomized) and observational studies (cohort, case-control, cross-sectional) consisting of pediatric patients, all of whom or the vast majority of whom were diagnosed with drug-resistant epilepsy according to the diagnostic criteria of the International League against Epilepsy (ILAE) who were placed on polytherapy regimens with valproate plus lamotrigine. (3) Comparative studies were eligible if they included either (a) a control group receiving an alternative antiseizure medication regimen (e.g., sodium valproate monotherapy or another non-lamotrigine regimen), or (b) predefined prognostic or clinical subgroups within patients receiving sodium valproate plus lamotrigine (e.g., MRI abnormality versus no MRI abnormality), provided that outcomes for the sodium valproate–lamotrigine combination could be extracted separately. (4) Report of both safety and efficacy outcomes including seizure freedom and $\geq$50% seizure reduction, changes in seizure frequency, adverse events, treatment discontinuation, and serious adverse events. (5) Studies published in English or translated into English. Any study that did not meet the above inclusion criteria was excluded.

2.5. Population

We included pediatric patients with epilepsy aged less than or equal to 18 years who were diagnosed with epilepsy according to the diagnostic criteria of the International League against Epilepsy (ILAE). Studies including both pediatric and adult patients were considered eligible if pediatric data could be extracted separately. Studies containing predominantly pediatric populations (mean/median age $\leq$ 18 years) were included if individual patient-level data for adults could not be extracted separately.

2.6. Intervention

The treatment group received sodium valproate combined with lamotrigine while the comparator group received sodium valproate alone, or sodium valproate with an anti-epileptic drug other than lamotrigine.

2.7. Comparison

Comparative studies included either pediatric patients receiving an alternative anti-seizure medication regimen (e.g., sodium valproate monotherapy or other non-lamotrigine regimens), or prognostic or clinical subgroups of patients receiving sodium valproate plus lamotrigine, such as stratification according to neuroimaging findings or other baseline clinical characteristics, where subgroup-specific outcomes were reported.

2.8. Outcome

Our primary outcomes were total treatment effect defined as ≥50% seizure reduction, and seizure freedom. Secondary outcomes included changes in seizure frequency, incidence of adverse events, and treatment discontinuation.

2.9. Data Extraction

Two reviewers independently extracted data from the included studies using a standard data extraction form and the information extracted included the following factors: study characteristics including year, country, design, study type as either single arm or comparative study, total sample size, sample size of each group, recruitment period, follow-up duration, intervention group and the therapy given with doses, control group and the therapy given with doses, is study completed or terminated with reasons of termination; patient demographics including age, sex, and type of epilepsy; outcomes characteristics including total treatment effect defined as ≥50% seizure reduction, seizure freedom, changes in seizure frequency, incidence of adverse events and treatment discontinuation.

2.10. Quality and Risk-of-Bias Assessment

Methodological quality and risk of bias were assessed according to study design using design-appropriate instruments. The Cochrane Risk of Bias 2 (RoB 2) tool was used for the randomized comparative study, whereas the Newcastle–Ottawa Scale (NOS) was applied to observational studies. CASP and SIGN checklists were additionally used as complementary methodological appraisal frameworks. These instruments were used to characterize study-level methodological limitations and were not combined to generate an overall certainty rating for the body of evidence. Given the predominantly observational evidence base and the limited number of contributing studies, no overall certainty category was assigned using an informal or non-validated approach.

2.11. Statistical Analysis

For single-arm studies, pooled proportions were calculated for the study outcomes. Proportions were transformed using the Freeman–Tukey double-arcsine transformation to stabilize variances before pooling. As a sensitivity analysis, pooled proportions were additionally estimated using a binomial generalized linear mixed-effects model with study-specific random intercepts to assess the robustness of the results to the choice of meta-analytic method, particularly given the small number of contributing studies. For comparative studies, pooled risk ratios (RR) with 95% confidence intervals (CIs) were calculated. A random-effects meta-analysis (DerSimonian–Laird method) was used to estimate pooled prevalence. Heterogeneity was assessed using the I^2 statistic: Low (<25%), Moderate (25–50%), and High (>50%). For this study, significant heterogeneity was set at >50% or $p < 0.1$. Publication bias was planned to be assessed using funnel plots and Egger's

regression when at least 10 studies were available. Sensitivity analyses were conducted to assess the robustness of the pooled single-arm estimates and to explore potential sources of heterogeneity.

3. Results

3.1. Literature Search

A comprehensive systematic search across major electronic databases including PubMed, Medline, Scopus, Embase, Web of Science, Google Scholar, PubMed Central, ScienceDirect, Cochrane Library, and clinicaltrials.gov yielded a total of 562 potentially relevant studies. After removal of 212 duplicate records out of the 562 studies, the titles and abstracts of the remaining 350 articles were screened independently by two reviewers. Of these, 315 records were excluded based on abstract screening as they failed to meet baseline inclusion criteria. The remaining 35 articles underwent detailed full eligibility assessment, and only 7 articles met the inclusion and exclusion criteria and were included in the study; the remaining 28 articles were excluded. Critical appraisal was applied to all 7 included studies [17–23] and was assessed as either moderate or high quality. All included studies were published between 2003 and 2025, capturing data on the safety and efficacy of sodium valproate (VPA) and lamotrigine (LTG) polytherapy. The entire systematic literature search and selection of final records is illustrated in the PRISMA 2020 flow diagram (Figure 1) below.

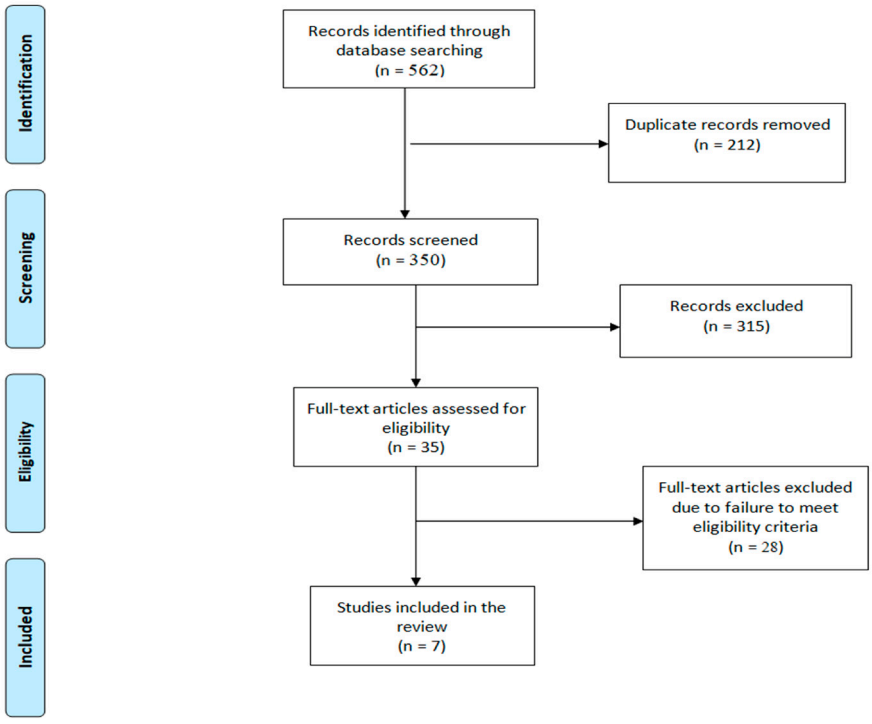

Figure 1. PRISMA Flow Diagram for Study Selection.

3.2. Study Characteristics

Overall, the included studies were published between 2003 and 2025 and originated primarily from South America (Brazil), Asia (China, Japan, India), and multinational pediatric epilepsy cohorts. Five studies were single-arm investigations evaluating the efficacy and safety of sodium valproate plus lamotrigine polytherapy. Two studies employed comparative designs. One directly compared sodium valproate plus lamotrigine with sodium valproate monotherapy, contributing to the therapeutic comparative meta-analysis. The second stratified patients receiving the same combination therapy according to baseline MRI

findings (MRI abnormality versus no MRI abnormality) and was included as a prognostic subgroup study to explore factors associated with treatment response but was not pooled in comparative efficacy analyses because both groups received the same intervention. Total sample sizes for the individual studies ranged from 20 patients in the Indian cohort to 177 patients in the multinational clinical trial, while the specific VPA + LTG subcohorts ranged from 16 to 59 patients. The included investigations comprised 3 retrospective observational studies, 2 prospective cohort studies, 1 mixed retrospective–prospective study, and 1 randomized comparative clinical trial. The randomized clinical trial study evaluates adjunctive lamotrigine (LTG) added to any background AED regimen. It is not a pure clinical trial strictly evaluating the valproate (VPA) + LTG combination across the entire sample; however, the paper explicitly tracks and reports data for a distinct subgroup taking concomitant valproate only (n = 16), representing our dual therapy intervention group, which, therefore, met our inclusion criteria via subgroup data extraction. However, the paper was only used for qualitative synthesis and was not involved in quantitative synthesis because the outcomes reported were for the general sample population. Therefore, the paper was considered in this study as supportive subgroup evidence rather than a randomized trial directly testing the VPA + LTG combination. The principal characteristics of the included studies are summarized in Table 1 below.

Table 1. Characteristics of the Included Studies.

Study	Year	Country	Design	Study Type	Sample Size (Subcohort)	Intervention (Sample Size)	Comparator (Sample Size)
Grisotto et al. [17]	2008	Brazil	Retrospective	Single arm	37	VPA + LTG	None
Thome–Souza et al. [18]	2013	Brazil	Prospective	Single arm	51	VPA + LTG	None
Zhang et al. [19]	2020	China	Prospective	Comparative	110 (59/51)	VPA + LTG	VPA alone
Watanabe et al. [20]	2025	Japan	Retrospective	Prognostic subgroup study	21	VPA + LTG	MRI abnormality vs. no MRI abnormality
Thome–Souza et al. [21]	2003	Brazil	Retrospective	Single arm	28	VPA + LTG	None
Jain et al. [22]	2011	India	Retrospective + prospective	Single arm	20	VPA + LTG	None
Piña–Garza et al. [23]	2008	Multinational	Post-hoc observational subgroup of RCT	Interventional clinical trial	177 (16)	VPA + LTG	Placebo

Across the studies, the sample age profile ranged from infants as young as 1 month old to older adolescents up to 22 years of age, with median or mean ages in most cohorts clustering between 6 and 12 years. Gender distribution showed a consistent male predominance in the majority of the literature, ranging from a slight majority of 57.6% male in the study group by Zhang et al., 2020 [19] up to a distinct 85% male majority in the cohort by Jain et al., 2011 [22], though Thomé–Souza et al., 2003 [21] reported a slight female predominance at 52.9%. Clinically, every included study uniformly evaluated variants of refractory, intractable, or drug-resistant childhood epilepsy. The specific classification

of these baseline epilepsy profiles varied, spanning primarily generalized seizures, drug-resistant focal epilepsy (DRFE), secondarily generalized variants, and specific childhood epilepsy syndromes such as Lennox–Gastaut syndrome. The clinical follow-up duration was highly variable across the study designs; it ranged from hyperacute and short-term windows of 6 months to 12 months in the comparative frameworks by Zhang et al., 2020 and Watanabe et al., 2025 [19,20], up to long-term longitudinal surveillance spanning 2 to 4 years total in the observational single-arm cohorts. Table 2 below summarizes the basic demographic data of the included studies.

Table 2. Basic Demographic Characteristics of the Included Studies.

Study	Age in Years: Mean (Range)	Sex: Male (%)/Female (%)	Type of Epilepsy	Follow-Up Duration: Median
Grisotto et al. [17]	12 (3–22)	25 (67.5%)/12 (32.5%)	Refractory epilepsy (84% primarily generalized, 16% partial)	Not explicitly stated
Thome–Souza et al. [18]	8 (4–16)	24 (47.1%)/27 (52.9%)	Refractory epilepsy (31.4% generalized, 68.6% partial)	2 years
Zhang et al. [19]	6.18 (3–12)	34 (57.6%)/25 (42.4%)	Refractory epilepsy (Partial, generalized, secondarily generalized, and Lennox–Gastaut syndrome)	6 months
Watanabe et al. [20]	8 (1.8–13.9)	16 (76%)/5 (24%)	Drug-resistant focal epilepsy (DRFE)	12 months
Thome–Souza et al. [21]	8.6 (4–16)	16 (57.1%)/12 (42.9%)	Refractory epilepsy (50% generalized, 50% focal)	2 years
Jain et al. [22]	7.5 (2.4–16.6)	17 (85%)/3 (15%)	Refractory epilepsy (Myoclonic, GTC, partial, atonic, absence)	7.9 months
Piña–Garza et al. [23]	1.1 (0.08–2)	52%/48% (Not specified for subcohort)	Refractory/uncontrolled partial seizures	Varied (4–8 weeks)

3.3. Quality and Risk of Bias Assessment

The methodological quality and risk of bias of the included studies were assessed using design-appropriate appraisal tools. The randomized comparative study was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, while observational studies were evaluated using the Newcastle–Ottawa Scale (NOS), with CASP and SIGN checklists used as complementary methodological appraisal frameworks. The assessments indicated variable methodological quality across the included studies, with the observational studies generally demonstrating moderate-to-good methodological characteristics but limitations related to retrospective designs, small sample sizes, incomplete reporting, and potential selection and information biases. The randomized comparative study was assessed separately using RoB 2, with the principal concerns relating to the limited number of participants and potential methodological limitations. These assessments were used to characterize study-level methodological quality and risk of bias and were not combined to assign an overall certainty rating to the body of evidence.

3.4. Publication Bias

Based on a rule of thumb proposed by the Cochrane Handbook for Systematic Reviews of Interventions, where it says that at least 10 studies should be available for appropriate bias assessment, we did not assess publication bias as only 7 studies in the literature met our eligibility criteria.

3.5. Primary Outcomes

3.5.1. Total Treatment Effect: Defined as ≥50% Reduction in Seizure Frequency

All seven included studies reported the overall therapeutic response following rational polytherapy with sodium valproate and lamotrigine. Five single-arm studies comprising 155 pediatric patients reported total treatment effect following treatment with sodium valproate plus lamotrigine. The pooled proportion of patients achieving an overall treatment response was 65.3% (95% CI 51.8-78.8%), with high heterogeneity (I^2 = 63.4%, p = 0.027). Only one comparative study involving 110 participants evaluated the total treatment effect. The sodium valproate plus lamotrigine combination provided preliminary comparative evidence of higher responder rates in a single comparative trial (48/59 [81.4%] vs. 31/51 [60.8%]), corresponding to a risk ratio (RR) of 1.34 (95% CI 1.04–1.72). This estimate represents evidence from a single observational study and therefore requires confirmation in larger randomized trials. Because only one comparative study was available, heterogeneity could not be estimated. However, in a randomized, double-blind, placebo-controlled trial (23), the authors separately reported outcomes for a predefined subgroup receiving concomitant valproate alone (n = 16), allowing indirect evaluation of the sodium valproate–lamotrigine combination. Within this subgroup, adjunctive lamotrigine demonstrated encouraging seizure control, with a median reduction in partial seizure frequency of 73.9%, 69% of patients achieving at least a 50% reduction in seizure frequency. Figure 2 below is a proportional forest plot for total treatment effect across the five single-arm studies.

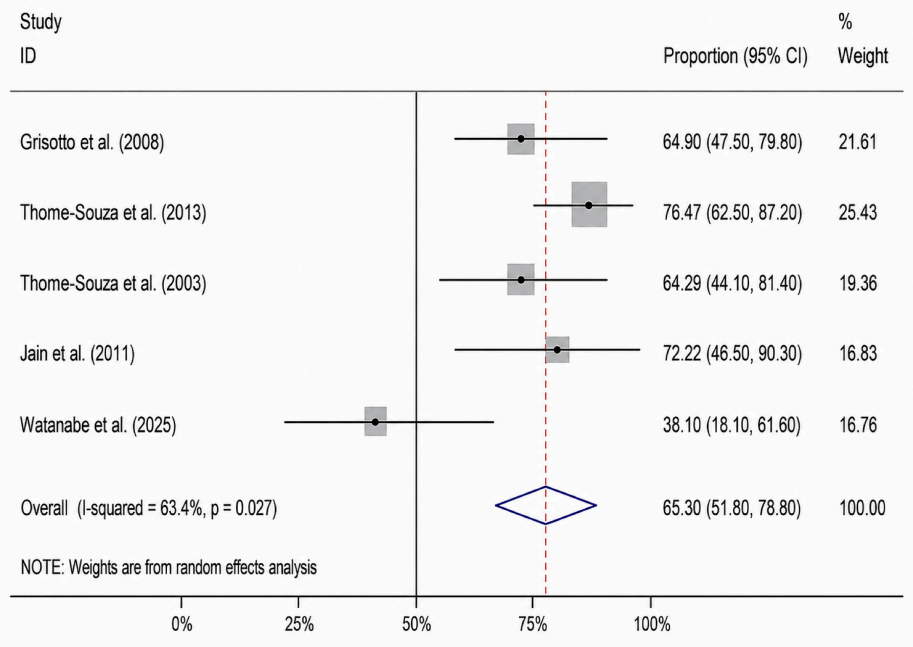

Figure 2. Forest Plot for Total Treatment Effect (≥50% Reduction in Seizure Frequency) [17,18,20–22].

3.5.2. Seizure Freedom

Complete seizure freedom was reported in all studies evaluating clinical efficacy. Across five single-arm studies (n = 155), the pooled seizure freedom rate was 24.8% (95% CI 18.0–31.6%), with no observed heterogeneity (I^2 = 0.0%, p = 0.886), indicating excellent consistency among studies. One comparative study reported seizure freedom. Complete seizure control occurred in 39.0% (23/59) of patients receiving sodium valproate plus lamotrigine compared with 29.4% (15/51) receiving sodium valproate alone (RR 1.33, 95% CI 0.78–2.26). The difference did not reach statistical significance. Heterogeneity was not estimable because only one study contributed data. Table 3 below summarizes the primary outcomes of the included studies. Additionally, in a study by Piña–Garza et al. (23), within

the subgroup receiving concomitant valproate alone, 25% of the patients became seizure-free during the open-label treatment phase. Figure 3 below is a proportional forest plot for seizure freedom across the five single-arm studies.

Table 3. Summary of the Primary Outcomes of the Included Studies.

Study	≥50% Seizure Reduction: Events/Total (%)	Seizure Freedom: Events/Total (%)
Comparative study		
Zhang et al., 2020 (Intervention) [19]	48/59 (81.4%)	23/59 (39.0%)
Zhang et al., 2020 (Control) [19]	31/51 (60.8%)	15/51 (29.4%)
Single-arm studies		
Grisotto et al., 2008 [17]	24/37 (64.9%)	9/37 (24.3%)
Thome–Souza et al., 2013 [18]	39/51 (76.5%)	15/51 (29.4%)
Thome–Souza et al., 2003 [21]	18/28 (64.3%)	6/28 (21.4%)
Jain et al., 2011 [22]	13/18 (72.2%)	5/18 (27.8%)
Watanabe et al., 2025 [20]	8/21 (38.1%)	4/21 (19.0%)

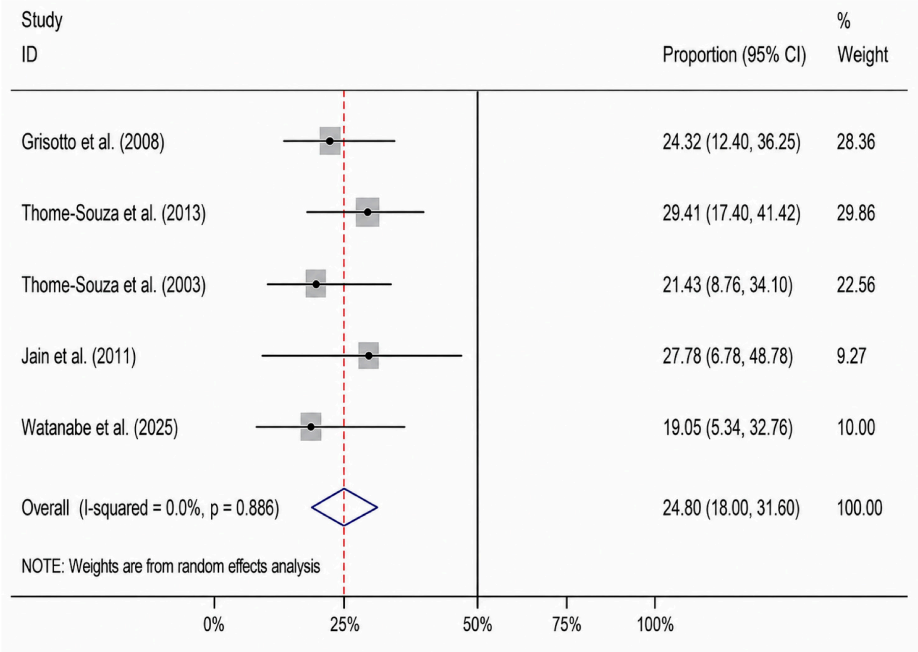

Figure 3. Forest Plot for Seizure Freedom [17,18,20–22].

3.6. Secondary Outcomes

3.6.1. Changes in Seizure Frequency

Quantitative continuous seizure frequency data were inconsistently reported across the included studies. Only one comparative study, Zhang et al., 2020 [19], provided precise continuous baseline and post-treatment values expressed as mean monthly seizure frequency (±SD). In this study, mean monthly seizure frequency in the sodium valproate plus lamotrigine group decreased from 15.89 ± 1.04 at baseline to 1.88 ± 0.60 post-treatment (a mean reduction of 14.01 seizures/month). In contrast, the sodium valproate monotherapy control group decreased from 15.43 ± 2.29 to 6.97 ± 1.15 seizures/month (a mean reduction of 8.46 seizures/month). The net difference in baseline-to-endpoint seizure reduction was

5.55 additional seizures reduced per month in favor of combination polytherapy. The post-treatment mean difference between groups was −5.09 seizures per month (95% CI: −5.44 to −4.74). Continuous seizure counts could not be quantitatively meta-analyzed across studies due to incompatible reporting units and inconsistent data presentation. Included studies evaluated seizure frequency over differing observation windows ranging from daily logs to monthly averages, which prevents accurate pooling without raw patient-level data. Furthermore, most single-arm cohorts reported outcomes solely as categorical responder rates (e.g., ≥50% reduction or seizure freedom) rather than continuous means and standard deviations. Consequently, continuous seizure reductions are presented descriptively from the single available comparative trial, which aligns with the primary binary outcome favoring combination polytherapy.

3.6.2. Incidence of Adverse Events

Safety outcomes were reported in all included studies. Overall, sodium valproate plus lamotrigine was well tolerated, and most reported adverse events were mild to moderate in severity. The most frequently reported treatment-emergent adverse events included dizziness, somnolence, fatigue, gastrointestinal disturbances, nausea, vomiting, headache, behavioral changes, ataxia, diplopia, and cutaneous rash. Cutaneous reactions represented the most clinically important adverse event because of the known pharmacokinetic interaction between sodium valproate and lamotrigine. However, the majority of skin reactions were mild and resolved following dose adjustment or treatment discontinuation. Serious dermatological complications such as Stevens–Johnson syndrome or toxic epidermal necrolysis were not consistently reported across the included studies. Five single-arm studies reported adverse events in 157 children. The pooled adverse event rate was 18.1% (95% CI 8.3–28.0%), with high heterogeneity (I^2 = 64.3%, p = 0.024). One comparative study evaluated adverse events. The incidence was 15.3% (9/59) in the combination therapy group and 31.4% (16/51) in the monotherapy group, corresponding to an RR of 0.49 (95% CI 0.24–1.00). Although this single comparative study reported fewer adverse events in the VPA + LTG group, the confidence interval included the null value and the evidence came from a single study. Therefore, the finding should be regarded as preliminary and hypothesis-generating, not as evidence that combination therapy has a superior safety profile. Heterogeneity could not be estimated. Table 4 below represents a summary of the secondary outcomes. Adverse events were reported using heterogeneous surveillance approaches across studies. Zhang et al., 2020 [19] used active clinical and laboratory monitoring, whereas Thome–Souza et al., 2013 [18] used structured follow-up; Grisotto et al., 2008 [17], Thome–Souza et al., 2003 [21], and Jain et al., 2011 [22] predominantly relied on patient or caregiver reporting. The reported adverse-event rates ranged from 7.8% to 35.7%, and the pooled incidence was 18.1% (95% CI 8.3–28.0%), with substantial heterogeneity (I^2 = 64.3%). Figure 4 below is a proportional forest plot for the incidence of adverse events across the five single-arm studies.

Table 4. Summary of the Secondary Outcomes of the Included Studies.

Study	Assessment Interval for Seizure Frequency	Changes in Seizure Frequency	Adverse Events: Events/Total (%)	Adverse Event Surveillance Method	Treatment Discontinuation: Events/Total (%)
Comparative study					
Zhang et al., 2020 (Intervention) [19]	Monthly (seizures/month)	Baseline 15.89 ± 1.04 → 1.88 ± 0.60 (post-treatment)	9/59 (15.3%)	Active clinical and laboratory monitoring	Not reported
Zhang et al., 2020 (Control) [19]	Monthly (seizures/month)	Baseline 15.43 ± 2.29 → 6.97 ± 1.15 (post-treatment)	16/51 (31.4%)	Active clinical and laboratory monitoring	Not reported

Table 4. *Cont.*

Study	Assessment Interval for Seizure Frequency	Changes in Seizure Frequency	Adverse Events: Events/Total (%)	Adverse Event Surveillance Method	Treatment Discontinuation: Events/Total (%)
Single-arm studies					
Grisotto et al., 2008 [17]	Seizure frequency per month	24/37 improved (64.9%)	4/37 (10.8%)	Passive self/caregiver reporting	0/37 (0.0\%)
Thome–Souza et al., 2013 [18]	Seizure frequency per month	39/51 improved (Year 1); 36/39 maintained (Year 2)	4/51 (7.8%)	Active structured follow-up	12/51 (23.5%)
Thome–Souza et al., 2003 [21]	Seizure frequency per month	18/28 improved (64.3%)	10/28 (35.7%)	Passive self/caregiver reporting	7/28 (25.0%)
Jain et al., 2011 [22]	Weekly to monthly seizure diaries	13/18 improved (72.2%)	5/20 (25.0%)	Passive self/caregiver reporting	6/20 (30.0%)
Watanabe et al., 2025 [20]	Seizure frequency per month	8/21 improved (38.1%)	5/21 (23.8%)	Active medical record tracking	3/21 (14.3%)

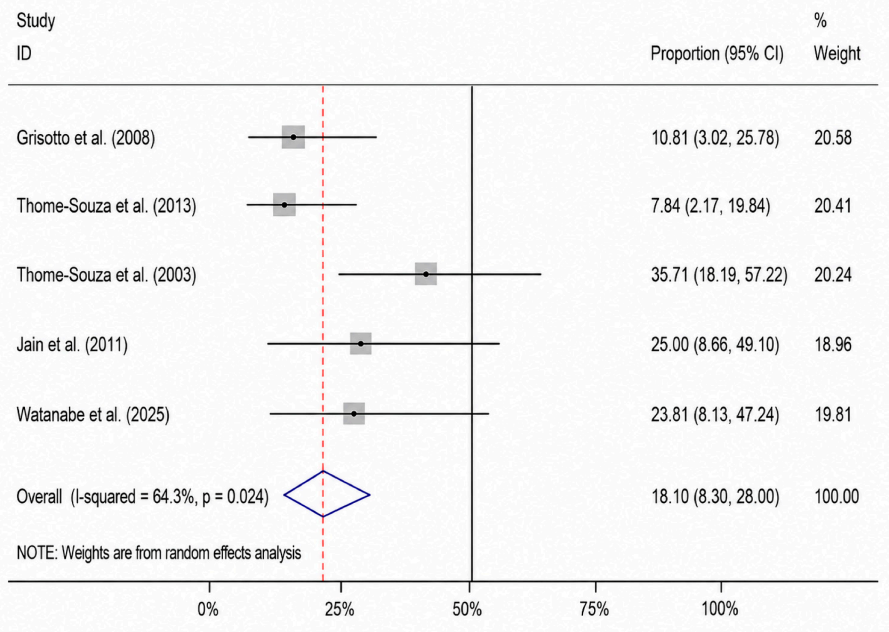

Figure 4. Forest Plot for Incidence of Adverse Event [17,18,20–22].

3.6.3. Treatment Discontinuation

Treatment discontinuation was reported in single-arm studies and occurred infrequently. Most studies reported high treatment adherence throughout follow-up, reflecting the acceptable tolerability and favorable clinical response associated with the sodium valproate–lamotrigine combination. Importantly, several studies noted that adverse effects resolved after dose adjustment without necessitating permanent discontinuation, emphasizing the importance of gradual lamotrigine titration in children receiving concomitant sodium valproate. The combined rate of treatment cessation due to side effects or therapeutic failure was 15.6% (95% CI: 7.2% to 30.4%). High heterogeneity was noted for this outcome (I^2 = 74.2%), marking distinct variations in institutional discontinuation protocols, ranging from 0.0% in Brazil (2008) to 30.0% in India (2011). Table 5 below summarizes the quantitative outcomes.

Table 5. Summary of Quantitative Findings (Abbreviations: RR, risk ratio; CI, confidence interval; I^2, Higgins heterogeneity statistic; NE, not estimable). NB: sample size slightly differed between primary and secondary outcomes (155 vs. 157) because 2 patients dropped out of the study due to early adverse events in Jain et al., 2011 [22], thus excluded for efficacy assessment.

Study Design and Target Outcomes	No. of Studies (N)	Patient Sample (n)	Pooled Estimate [95% CI]	Heterogeneity (I^2)
Comparative Arm (RRs/MD)				
Total Treatment Effect	1	110	RR: 1.34 [1.04, 1.72]	NA
Seizure Freedom	1	110	RR: 1.33 [0.78, 2.26]	NA
Changes in Seizure Freq.	1	110	MD: −5.09 [−5.44, −4.74]	NA
Incidence of Adverse Events	1	110	RR: 0.49 [0.24, 1.00]	NA
Single-Arm (Proportions)				
Total Treatment Effect	5	155	65.3% [51.8%, 78.8%]	63.4%
Seizure Freedom	5	155	24.8% [18.0%, 31.6%]	0.0%
Incidence of Adverse Events	5	157	18.1% [8.3%, 28.0%]	64.3%
Treatment Discontinuation	5	157	15.6% [7.2%, 30.4%]	74.2%

3.7. Leave-One-out Sensitivity Analysis

Sensitivity analyses demonstrated that the pooled estimates were generally robust, while identifying specific contributors to heterogeneity. For treatment response (≥50% seizure reduction), pooled estimates remained approximately 60–71%; exclusion of Watanabe et al., 2025 [20] which reported the lowest response rate (38.1%), or exclusion of the two short-follow-up studies, Jain et al., 2011 [22] and Watanabe et al., 2025 [20], increased the pooled response to approximately 71% and reduced heterogeneity to 0%, whereas exclusion of Grisotto et al., 2008 [17] or Jain et al., 2011 [22] did not eliminate substantial heterogeneity. For adverse events, excluding Thome–Souza et al., 2003 [21], which reported the highest event rate, reduced the pooled incidence from 18.1% to approximately 13% and I^2 from 64.3% to approximately 36%. For treatment discontinuation, exclusion of Grisotto et al., 2008 [17] which reported no discontinuations, increased the pooled estimate from 15.6% to approximately 23% and reduced I^2 from 74.2% to 0%. Overall, these analyses supported the robustness of the principal efficacy findings while indicating that heterogeneity was partly attributable to identifiable study-level differences; comparative sensitivity analyses were not possible because only one study contributed quantitative comparative data.

3.8. Sensitivity Analysis Using a Generalized Linear Mixed Model

To assess the robustness of the pooled proportions to the choice of meta-analytic method, sensitivity analyses were performed using a binomial generalized linear mixed-effects model with study-specific random intercepts. The alternative model produced estimates broadly consistent with the primary Freeman–Tukey double-arcsine/DerSimonian–Laird analysis. The pooled proportion achieving ≥50% seizure reduction was 63.7% (95% CI 56.1–70.7%), compared with 65.3% (95% CI 51.8–78.8%) in the primary analysis. The pooled proportion achieving seizure freedom was 25.2% (95% CI 19.1–32.4%), compared with 24.8% (95% CI 18.0–31.6%). The pooled incidence of adverse events was 20.6% (95% CI 14.9–27.6%), compared with 18.1% (95% CI 8.3–28.0%), while the pooled treatment-discontinuation rate was 19.9% (95% CI 14.6–26.3%), compared with 15.6% (95%

CI 7.2–30.4%). Overall, the alternative GLMM approach yielded estimates of similar magnitude and did not materially alter the direction or clinical interpretation of the primary findings, supporting the robustness of the results to the choice of statistical method.

4. Discussion

To the best of our knowledge, this systematic review and meta-analysis is the first quantitative synthesis specifically evaluating the efficacy and safety of rational polytherapy with sodium valproate (VPA) and lamotrigine (LTG) in children with drug-resistant epilepsy (DRE). Across seven eligible studies, our findings demonstrate that this combination therapy is associated with favorable seizure outcomes, with approximately two-thirds of children achieving a clinically meaningful response (≥50% seizure reduction) and approximately one-quarter attaining complete seizure freedom. Moreover, comparative evidence demonstrated significantly greater overall treatment response with a VPA–LTG polytherapy regimen than with sodium valproate alone, while maintaining an acceptable safety profile characterized predominantly by mild-to-moderate adverse events. Considering the refractory nature of the epilepsy in the included cohorts, the pooled treatment response of approximately 65% is clinically important and suggestive of overall observed clinical response. However, it does not indicate a definitive measure of efficacy because it was derived predominantly from single-arm observational cohorts, which cannot establish treatment superiority, causal effectiveness, or benefit over alternative ASM strategies because there was no untreated or contemporaneous comparator. Children with DRE frequently continue to experience seizures despite multiple appropriately selected antiseizure medications, and therapeutic options become progressively limited after failure of two adequately dosed drugs. Previous longitudinal studies have demonstrated that the probability of achieving seizure freedom declines substantially after failure of successive antiseizure medications, making any intervention capable of producing seizure reduction in this population particularly valuable [24,25]. Therefore, the observed response rate suggests that rational polytherapy combining VPA and LTG represents an effective treatment strategy for a substantial proportion of pediatric patients with otherwise refractory seizures.

Our comparative analysis demonstrated a significantly higher likelihood of achieving ≥50% seizure reduction with VPA-LTG polytherapy compared with sodium valproate alone (RR 1.34, 95% CI 1.04–1.72). Although only one comparative study contributed to this analysis, the finding is biologically plausible and consistent with the established concept of rational polytherapy advocated by Brodie and Sills, who proposed that combining antiseizure medications with complementary mechanisms of action improves efficacy while minimizing overlapping toxicity [26]. The overall therapeutic effect of the VPA + LTG combination regimen is derived from the reciprocal synergy that targets refractory seizure networks more robustly than single-agent pathways. Sodium valproate exerts broad-spectrum antiseizure activity through enhancement of GABAergic neurotransmission, modulation of voltage-gated sodium channels, and inhibition of T-type calcium channels, whereas lamotrigine predominantly inhibits voltage-dependent sodium channels and suppresses excessive glutamate release. These complementary mechanisms allow simultaneous modulation of inhibitory and excitatory neuronal pathways, thereby increasing the likelihood of disrupting epileptic network synchronization more effectively than either agent alone [27]. Beyond classical pharmacodynamic complementarity, accumulating evidence suggests that both sodium valproate and lamotrigine possess anti-inflammatory and neuroprotective properties that may further contribute to seizure control. Increasing recognition of epilepsy as a disorder involving both neuronal hyperexcitability and chronic neuroinflammation has shifted therapeutic attention toward immunomodulatory mech-

anisms. Experimental studies have demonstrated that valproate suppresses activation of nuclear factor-kappa B (NF-κB), reduces production of pro-inflammatory cytokines including interleukin-1β and tumor necrosis factor-α, and inhibits histone deacetylases involved in inflammatory gene transcription. Lamotrigine has similarly been shown to attenuate microglial activation, reduce oxidative stress, and suppress inflammatory signaling pathways implicated in epileptogenesis [15,28]. The combined anti-inflammatory effects of these two agents may therefore complement their antiseizure mechanisms, particularly in children whose pharmacoresistance is partly driven by persistent neuroimmune activation.

The pooled seizure freedom rate of approximately 25% deserves particular attention. Complete seizure freedom remains the ultimate therapeutic goal because even infrequent seizures continue to adversely affect neurodevelopment, cognition, educational attainment, and quality of life. Although our comparative analysis did not demonstrate a statistically significant superiority of combination therapy over monotherapy for seizure freedom, the point estimate consistently favored VPA-LTG polytherapy. The absence of statistical significance most likely reflects inadequate statistical power due to the availability of only one comparative study rather than true absence of benefit. Importantly, the remarkably low heterogeneity (I^2 = 0%) observed across the single-arm studies indicates consistent seizure freedom rates despite differences in study design, follow-up duration, and patient populations, suggesting that this finding is reproducible across diverse clinical settings. One notable observation was the substantial reduction in seizure frequency reported in the comparative study. Mean seizure frequency decreased by almost 90% following VPA-LTG combination therapy compared with a considerably smaller reduction in the monotherapy group. Although this outcome could not be quantitatively pooled, it provides clinically meaningful evidence that the combination not only increases responder rates but may also substantially reduce seizure burden. Such reductions have important implications because decreasing seizure frequency has been associated with improved cognitive performance, behavioral outcomes, school attendance, caregiver quality of life, and reduced healthcare utilization even in patients who do not achieve complete seizure remission [29,30].

Safety remains a major consideration when combining antiseizure medications, particularly in children. Our pooled adverse event rate of approximately 18% indicates that VPA–LTG polytherapy is generally well tolerated. Most adverse events were mild or moderate and consisted primarily of dizziness, somnolence, gastrointestinal symptoms, headache, behavioral disturbances, and transient cutaneous reactions. These findings are consistent with large observational studies demonstrating that adverse events associated with lamotrigine are largely dose-dependent and frequently improve following gradual titration or dosage adjustment [31]. Importantly, despite the well-recognized pharmacokinetic interaction whereby valproate inhibits lamotrigine glucuronidation and substantially prolongs its elimination half-life, serious dermatological complications such as Stevens–Johnson syndrome were uncommon across the included studies. This likely reflects increasing adherence to contemporary recommendations advocating slow lamotrigine titration and lower starting doses when administered concurrently with valproate [32]. Interestingly, the comparative study demonstrated a lower incidence of adverse events in the combination therapy group than in patients receiving sodium valproate monotherapy. Although this finding reached only borderline statistical significance, it supports the principle that rational polytherapy may permit effective seizure control using lower doses of individual drugs, thereby reducing dose-related toxicity despite increasing the number of medications administered. This concept has been emphasized in several contemporary reviews of antiseizure pharmacotherapy, which argue that appropriate drug selection is often more important than simply minimizing the number of medications prescribed [33,34]. Beyond neurological and cutaneous reactions, valproate requires attention to hepatic, metabolic,

endocrine, reproductive, and teratogenic risks, including weight gain and menstrual or polycystic ovary syndrome–related abnormalities in adolescent girls. Its use in females who may become pregnant warrants careful individualized risk–benefit assessment because of its comparatively high fetal malformation and neurodevelopmental risks. In addition, because valproate inhibits lamotrigine clearance and increases its exposure, lamotrigine should be initiated at a low dose and titrated slowly to reduce the risk of serious cutaneous reactions [35]. Pediatric case reports have documented SJS following concomitant VPA–LTG therapy in children, as well as metabolic complications such as symptomatic hypocalcemia during long-term treatment. These reports reinforce the importance of slow LTG titration, clinical monitoring, and prompt discontinuation when serious adverse reactions occur [36,37].

Emerging evidence suggests that oxidative stress and neuroinflammation form a reciprocal pathogenic network that may contribute to seizure persistence and epileptogenesis, providing a rationale for adjunctive strategies targeting redox signaling in addition to conventional antiseizure mechanisms. NOX2, a major source of seizure-associated reactive oxygen species (ROS), has emerged as a promising target, with preclinical studies showing that selective NOX2 inhibition can reduce ROS generation, neuroinflammation, neuronal injury, seizure susceptibility, and epileptogenesis. Complementary approaches aimed at enhancing endogenous antioxidant defenses, particularly activation of the Keap1/Nrf2/ARE pathway and modulation of the thioredoxin/thioredoxin reductase system, have likewise demonstrated reductions in oxidative stress, inflammatory signaling, seizure severity, and disease progression in experimental models. Collectively, these findings suggest that simultaneously reducing ROS production and strengthening endogenous antioxidant capacity may offer a broader disease-modifying strategy capable of interrupting the oxidative stress–neuroinflammation–epileptogenesis cycle. However, these approaches remain investigational, as current evidence is predominantly derived from cellular and animal studies; their efficacy, safety, optimal timing, and ability to modify epilepsy in humans require confirmation in well-designed clinical studies [38–40]. Drug-resistant epilepsy is mechanistically heterogeneous, and immune-mediated mechanisms may contribute to pharmacoresistance in a subset of patients with otherwise unexplained intractable epilepsy. Recent evidence has identified circulating antibodies against glutamate-receptor epitopes, including AMPA-GluR3B and NMDA receptor peptides, with experimental evidence suggesting potential neuronal injury and seizure-promoting effects; however, the clinical and pathogenic significance of these antibodies remains uncertain. Thus, failure of conventional antiseizure medications may occasionally reflect an underlying immune-mediated process rather than inadequate control of neuronal excitability alone, highlighting the potential value of autoimmune evaluation in selected patients with unexplained drug-resistant epilepsy [41].

Our findings have several important clinical implications. Current international epilepsy management increasingly emphasizes individualized treatment strategies based on seizure type, epilepsy syndrome, comorbidities, and pharmacological mechanisms rather than sequential empirical drug substitution. The present findings provide quantitative support for considering sodium valproate plus lamotrigine as one of the preferred rational polytherapy combinations in appropriately selected children with DRE, particularly when monotherapy has failed and epilepsy surgery or neuromodulation is unavailable or unsuitable. This may be especially relevant in low- and middle-income countries where access to advanced epilepsy surgery, ketogenic dietary programs, responsive neurostimulation, and newer high-cost antiseizure medications remains limited. Nevertheless, several limitations should be acknowledged. First, the evidence base is small and predominantly observational. Of the seven included studies, five were single-arm observational studies,

one was a comparative prospective study, and one was a randomized clinical trial that provided only a predefined subgroup relevant to concomitant valproate and lamotrigine therapy. The limited number of studies, relatively small sample sizes, variable follow-up durations, and differences in clinical settings substantially limit the certainty and generalizability of the evidence. Second, most included studies were observational, introducing potential risks of selection bias, residual confounding, and indication bias. Third, variability in epilepsy syndromes, treatment duration, outcome definitions, and follow-up periods contributed to between-study heterogeneity. Fourth, publication bias could not be formally assessed because fewer than ten studies were available. Fifth, insufficient data precluded subgroup analyses according to epilepsy syndrome, age, seizure type, lamotrigine dosage, valproate serum concentrations, or duration of treatment. Fifth, studies published prior to or around the 2010 ILAE consensus definition used legacy terminology such as "refractory", "intractable", or "uncontrolled". While these cohorts represented clinically treatment-resistant patients who had failed multiple prior antiseizure medications (ASMs), they may not strictly align with the formal 2010 ILAE criteria (failure of $\geq$2 appropriately chosen and tolerated ASM regimens). Sixth, the vast majority of the cohorts specifically evaluated VPA + LTG co-administration, whereas others used LTG as an add-on treatment in patients receiving VPA and, in a few cases, additional antiseizure medications. This might be an important source of clinical heterogeneity and limit the entire evidence base of the study as evidence for exclusive two-drug therapy. Finally, most studies originated from middle-income countries, potentially limiting generalizability to other healthcare settings.

Two of the included studies might further limit the generalization of our findings in this study. One included comparative study evaluated prognostic subgroups rather than alternative treatment regimens and therefore contributed only to the qualitative synthesis rather than pooled comparative meta-analyses. An additional randomized trial by Piña–Garza et al. provided supportive evidence for the effectiveness of concomitant valproate and lamotrigine, reporting substantial seizure reduction within a predefined valproate subgroup. However, because treatment allocation was randomized irrespective of background anti-epileptic therapy and the valproate subgroup analysis was not independently randomized, these data were excluded from quantitative pooling to minimize the risk of subgroup bias. Nevertheless, the favorable seizure outcomes observed in this subgroup are consistent with the overall findings of the present review and further support the potential synergistic effect of the sodium valproate–lamotrigine combination.

5. Conclusions

This systematic review and meta-analysis provides the first quantitative synthesis of the available evidence regarding rational polytherapy with sodium valproate and lamotrigine in pediatric drug-resistant epilepsy. The findings demonstrate that this combination is associated with a high overall treatment response, clinically meaningful seizure reduction, and acceptable tolerability, with approximately two-thirds of children achieving a $\geq$50% reduction in seizure frequency and one-quarter attaining complete seizure freedom. Comparative evidence further provided preliminary comparative evidence of higher responder rates in a single comparative trial, requiring confirmation in larger randomized trials. The favorable efficacy observed is biologically plausible given the complementary pharmacodynamic actions, well-recognized pharmacokinetic synergy, and emerging anti-neuroinflammatory and microglia-modulating properties of both agents, which may collectively address multiple mechanisms underlying pharmacoresistant epilepsy. Although the current evidence is limited by the small number of comparative studies, predominantly

observational study designs, and clinical heterogeneity among included populations, the consistency of the overall findings supports the use of this combination as an effective and generally well-tolerated rational polytherapy option for appropriately selected children with drug-resistant epilepsy. Future large, multicenter randomized controlled trials are needed. Although neuroinflammation and microglial activation are increasingly recognized as contributors to epileptogenesis and drug resistance, none of the included clinical studies directly assessed whether these mechanisms mediated the response to VPA–LTG therapy. Therefore, the proposed anti-inflammatory or microglia-modulating synergy should be regarded as a biologically plausible hypothesis rather than a demonstrated mechanism of treatment response. The clinical findings of this meta-analysis support the efficacy and safety of VPA–LTG, whereas confirmation of any underlying immunomodulatory effects will require prospective studies incorporating inflammatory and microglial biomarkers.

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