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Network Meta-Analysis of the Comparative Efficacy and Safety of Lamotrigine, Brivaracetam, Perampanel, and Cannabidiol for the Management of Focal Epilepsy

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 March 2025 and was last updated on 23 March 2025.

INTRODUCTION

Review question / Objective Population: This study exclusively included individuals with focal epilepsy, specifically those diagnosed with refractory partial-onset seizures (POS), uncontrolled POS, or refractory POS. Eligibility criteria required a minimum treatment duration of 10 weeks and baseline seizure frequency data, with no geographical restrictions. Intervention: The interventions were limited to various doses of orally administered LTG, BRV, PER, and CBD. Comparison: Control groups comprised alternative drugs, varying doses of the same drug, or placebo. Outcomes: The main results encompassed a 50% rate of response, decreased seizure occurrences, rates of no seizures, and the frequency of adverse events emerging from treatment(TEAEs). Study Design: Only RCTs were included.

Condition being studied Over the past few decades, more than 20 antiepileptic drugs (AEDs) have been developed, particularly newer-generation agents that offer improved seizure control with reduced adverse effects. Despite these advancements, refractory epilepsy remains incurable, and its management primarily depends on pharmacotherapy to mitigate seizure frequency and improve quality of life. AEDs are classified into three generations based on their time of market introduction rather than their molecular structures or mechanisms of action. First-generation AEDs, introduced between 1912 and 1970, include phenobarbital, primidone, phenytoin, ethosuximide, valproate, and carbamazepine . These agents present notable pharmacokinetic challenges, such as the zero-order kinetics of phenytoin, hepatic enzyme autoinduction by carbamazepine, high protein binding of phenytoin and valproate, and extensive metabolism via the cytochrome P450 enzyme system[7]. Second-generation AEDs, first introduced with felbamate in 1993, include gabapentin, lamotrigine (LTG), levetiracetam, oxcarbazepine, tiagabine, topiramate, pregabalin, zonisamide, vigabatrin, and clobazam[8]. Compared to first-generation AEDs, these agents exhibit superior pharmacokinetic

properties, such as high oral bioavailability, minimal protein binding, reduced cytochrome P450 metabolism, and predominant renal excretion [8]. Compared to first-generation AEDs, second-generation AEDs generally offer improved tolerability [9]. However, they are not without drawbacks, including lamotrigine-induced Stevens-Johnson syndrome, topiramate-associated cognitive dysfunction, zonisamide-induced nephrolithiasis, and tiagabine-related encephalopathy and nonconvulsive status epilepticus[9]. The third-generation AEDs, introduced with the approval of lacosamide in 2008, include eslicarbazepine acetate, rufinamide, brivaracetam (BRV),perampanel (PER),stiripentol, and retigabine . Despite continued progress in AED development, the optimal treatment strategy balancing efficacy and safety remains undetermined[11].

METHODS

Participant or population This study exclusively included individuals with focal epilepsy, specifically those diagnosed with refractory partial-onset seizures (POS), uncontrolled POS, or refractory POS. Eligibility criteria required a minimum treatment duration of 10 weeks and baseline seizure frequency data, with no geographical restrictions.

Intervention The interventions were limited to various doses of orally administered LTG, BRV, PER, and CBD.

Comparator Control groups comprised alternative drugs, varying doses of the same drug, or placebo.

Study designs to be included Only RCTs were included.

Eligibility criteria Population: This study exclusively included individuals with focal epilepsy, specifically those diagnosed with refractory partial-onset seizures (POS), uncontrolled POS, or refractory POS[4]. Eligibility criteria required a minimum treatment duration of 10 weeks and baseline seizure frequency data, with no geographical restrictions. Intervention: The interventions were limited to various doses of orally administered LTG, BRV, PER, and CBD. Comparison: Control groups comprised alternative drugs, varying doses of the same drug, or placebo. Outcomes: The main results encompassed a 50% rate of response, decreased seizure occurrences, rates of no seizures, and the frequency of adverse events emerging from treatment(TEAEs). Study Design: Only RCTs were included.

Information sources PubMed, EMBASE, Cochrane Library, Scopus, and Web of Science.

Main outcome(s) The main results encompassed a 50% rate of response, decreased seizure occurrences, rates of no seizures, and the frequency of adverse events emerging from treatment(TEAEs).

Quality assessment / Risk of bias analysis The Risk of Bias(ROB) instrument from the Cochrane Collaboration was utilized toassess the methodological soundness of the RCTs incorporated. The evaluation covered seven areas: generating sequences randomly, hiding allocation details, ensuring participants and staff were unaware, concealing the outcome evaluation, ensuring the data was complete, selective disclosure, and other possible biases. Every research was categorized based on its risk level: low, moderate, or high bias risk.

Strategy of data synthesis Assessing the efficacy of different interventions, a meta-analysis of the network was conducted utilizing a random-effects model in STATA 16, integrated with the network package.

Subgroup analysis For assessing the uniformity in direct versus indirect comparisons, a comprehensive inconsistency analysis was performed, utilizing the node-splitting technique to evaluate local discrepancies, where a p-value less than 0.05 denotes notable inconsistency. Intervention rankings were determined via the surface beneath the cumulative ranking curve (SUCRA), where elevated SUCRA scores(0–100%) signify enhanced efficacy. For assessing the uniformity in direct versus indirect comparisons, a comprehensive inconsistency analysis was performed, utilizing the node-splitting technique to evaluate local discrepancies, where a p-value less than 0.05 denotes notable inconsistency[19]. Intervention rankings were determined via the surface beneath the cumulative ranking curve (SUCRA), where elevated SUCRA scores(0–100%) signify enhanced efficacy. Cumulative ranking probability plots were constructed to provide a visual representation of the intervention rankings. Furthermore, funnel plots were created for every result to evaluate the likelihood of publication bias[21].

Sensitivity analysis To address the observed heterogeneity, a sensitivity analysis was conducted by sequentially excluding each study.

Country(ies) involved China/Dali Bai Autonomous Prefecture People's Hospital.

Keywords Lamotrigine, Brivaracetam, Perampanel, Cannabidiol, Network Meta-Analysis, Efficacy, Safety.

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