Efficacy and Safety of Antiseizure Medications in Lennox Gastaut Syndrome: A Network Meta-Analysis

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Background

Lennox Gastaut syndrome (LGS) is an age-dependent epileptic encephalopathy characterized by drug-resistant polymorphic seizures with an early age-onset, distinctive electroencephalographic findings (generalized slow spike-wave discharges), and cognitive impairment.

Objective

To assess the comparative efficacy and safety of antiseizure medications (ASMs) for the management of LGS.

Methods

- Checklist: Preferred Reporting Items for systematic review and Meta-analysis (PRISMA) statement
- Study Design: Randomized Controlled Trials (RCTs) and their open-label extension (OLE) studies.
- Population: LGS
- Intervention: CBD, CLB, FLB, LTG, RFM and TPM
- Comparator: ASMs or placebo
- Outcome:
  - Efficacy outcomes: ≥50%, ≥75%, and 100% reduction in drop seizures (tonic-atonic seizures)
  - Safety outcomes: Treatment emergent adverse events (TEAEs) and treatment withdrawal due to AEs

Search Terms: "anticonvulsive", "anti-seizure", "antiepileptic" and "Lennox Gastaut syndrome" → **Search Database PubMed and Embase**

Quality Assessment: Cochrane Risk of Bias 2.0 (ROB 2.0) for RCTs and methodological index for non-randomized studies (MINORS) (**Figure 1**)

Data Analysis

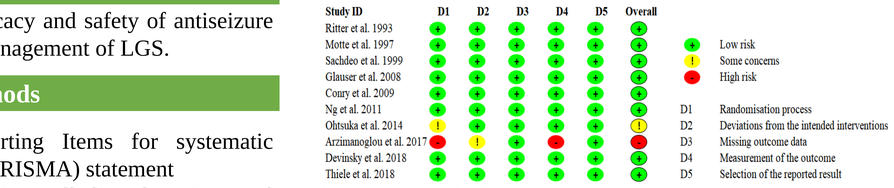
- Software: MS excel, Rstudio
- Random effects model and Odds ratio (OR) with 95% confidence interval (CI)
- Network plots: to visualize the geometry of the indirect and direct evidence.
- Surface under the cumulative ranking curve (SUCRA): to rank the treatments (p-score)

Abbreviations:- DB: double blinded; CBZ: carbamazepine; CBD_L: cannabidiol low dose (10 mg/kg/day); CLB_M: clobazam medium dose (0.50 mg/kg/day); CLB_L: clobazam low dose (0.25 mg/kg/day); CLM: clonazepam; ETS: ethosuximide; KD: ketogenic diet; LEV: levetiracetam; NTZ: nitrazepam; NR: not reported; OXC: oxcarbazepine; PHB: phenobarbital; PHT: phenytoin; VPA: valproic acid/ valproate; VGB: vigabatrin; ZNS: zonisamide

Results

- Fifteen studies including 1263 participants with LGS (aged 2-54 years) receiving any of six different ASMs [cannabidiol (CBD), clobazam (CLB), felbamate (FLB), lamotrigine (LTG), rufinamide (RFM), topiramate (TPM)] or placebo were included (**Table 1**).

Figure 1 : Quality assessment of RCT using ROB 2.0



Six included OLE had low risk of bias as assessed using MINORS

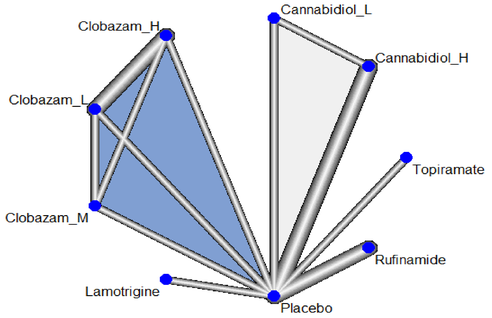


Figure 2: Network plot among the different ASMs in LGS

- CLB 1.0 mg/kg/day (CLB_H) [OR: 4.9; 95% CI: 2.3-10.8] was significantly associated with a ≥50% reduction in drop seizure frequency as compared with placebo and achieved the highest-ranking probability (0.89) based on SUCRA values, while CBD 20 mg/kg/day (CBD_H) [OR: 3.8; 95% CI: 1.6-9.0] had significantly higher odds for the occurrence of any TEAEs and had the highest ranking probability (0.85) (**Figure 3**).
- For long-term treatment with CLB [78%; 95% CI: 70-85%] was associated with a significantly higher proportion of patients with reduction in drop-seizures, and long-term use of CBD [96%; 95% CI: 95-98%] was associated with a higher frequency of TEAEs (**Table 2**).

Table 1: Baseline characteristics of included studies

Study	Design	Duration; Weeks	Participants	Age; Mean (SD)	Male; N (%)	Seizures Type	Intervention (N)	Concomitant Medication
Studies for short-term outcomes								
Ritter et al.	DB, RCT	10	73	13 (7.0)	51 (70)	Atonic	FLB (37); Placebo (36)	NR
Motte et al.	DB, RCT	16	169	10.3 (5.6)	99 (59)	Drop attacks	LTG (79); Placebo (90)	VPA, CBZ, PHT, OXC, CLB, VGB, CLM, PHB, ETS, NTZ, primidone
Sachdeo et al.	DB, RCT	11	98	11.2 (7.0)	53 (54)	Drop attacks	TPM (48); Placebo (50)	Not reported
Glauser et al.	DB, RCT	12	138	16.0 (8.0)	86 (62)	Tonic-atonic	RFM (74); Placebo (64)	VPA, TPM, LTG, CBZ, CLM
Conry et al.	DB, RCT	7	68	7.4*	42 (62)	Drop	CLB_H (36); CLB_L (32)	Not reported
Ng et al.	DB, RCT	15	238	12.4 (9.0)	144 (61)	Drop	CLB_H (59); CLB_M (62); CLB_L (58); Placebo (59)	VPA, VPA semisodium, VPA sodium
Ohtsuka et al.	DB, RCT	12	58	15.0 (6.6)	36 (62)	Tonic-atonic	RFM (28); Placebo (30)	VPA, CLB, LTG
Devinsky et al.	DB, RCT	14	225	15.6 (9.9)	129 (57)	Drop	CBD_H (76); CBD_L (73); Placebo (76)	VPA (all forms), CLB, LEV, LTG, KD, VNS, RFM
Thiele et al.	DB, RCT	14	171	15.4 (9.3)	88 (51)	Drop	CBD_H (86); Placebo (85)	VPA (all forms), CLB, LEV, LTG, KD VNS, RFM
Studies for long-term outcomes								
Glauser et al.	OLE	77**	97	11 (10.0)	52 (54)	Drop attacks	TPM	VPA
Kluger et al.	OLE	156	124	14.2 (8.3)	74 (60)	Tonic-atonic	RFM	VPA, CLM, LTG, PHT, CBZ, LEV, TPM, PHB
Conry et al.	OLE	156	267	11.3 (7.8)	163 (61)	Drop	CLB	VPA, LEV, LTG, TPM, diazepam, RFM, FLB, lorazepam, PHB, PHT, lacosamide, KD, VNS, ZNS
Ohtsuka et al.	OLE	123**	54	15.0 (6.8)	33 (61)	Tonic-atonic	RFM	VPA, CLB, LTG, PHT, CBZ, CLM
Patel et al.	OLE	156**	366	15.9 (9.5)	198 (54)	Drop	CBD	CLB, VPA, LTG, LEV, RFM
Arzimanoglou et al.	Open-label, RCT	106	37	28.8 (9.8)	24 (65)	Mixed	RFM (25); other ASMs (12)	VPA, LEV, TPM, diazepam, VGB, CLB, LTG, CLM, NTZ, OXC, ETS, PHB, ZNS, midazolam, primidone

* denotes median; ** denotes mean weeks

Figure 3: Ranking probability of ASMs for the treatment of LGS

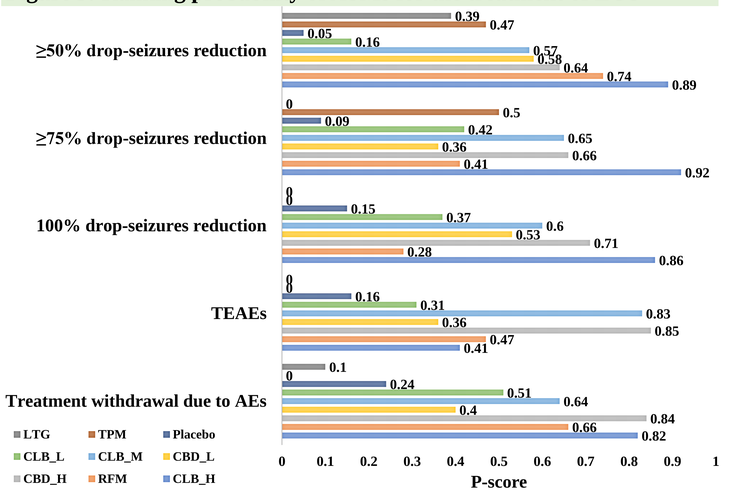


Table 2: Long-term efficacy of ASMs for the management of LGS

Drugs	No. of study	Responders	Proportion [95% CI]
≥50% drop-seizures reduction			
CBD	1	133/202	0.65 [0.59-0.72]
RFM	2	77/170	0.45 [0.38-0.53]
CLB	1	94/121	0.78 [0.70-0.85]
TPM	1	45/82	0.55 [0.44-0.66]
100% drop-seizures reduction			
CBD	1	16/202	0.08 [0.04-0.12]
RFM	2	12/170	0.07 [0.03-0.11]
CLB	1	46/121	0.38 [0.29-0.47]
TPM	1	12/82	0.15 [0.07-0.22]
Safety outcomes			
Treatment emergent adverse events			
CBD	1	353/366	0.96 [0.95-0.98]
CLB	1	246/267	0.92 [0.89-0.95]
RFM	3	189/203	0.94 [0.86-1.0]

Conclusion: CLB 1.0 mg/kg/day had the best efficacy and safety profile compared with other included ASMs. Future head-to-head trials comparing these ASMs are needed to understand their comparative efficacy and safety better.