Newer AEDs compared to LVT as adjunctive treatments for uncontrolled focal epilepsy

Dr. Yotin Chinvarun. M.D. Ph.D.
Chronology of antiepileptic drug introduction over the past 150 years

BDZ, benzodiazepines; BR, bromide; ESL, eslicarbazepine; ESM, ethosuximide; FBM, felbamate; GBP, gabapentin; LCM, lacosamide; LEV, levetiracetam; PGB, pregabalin; PRM, primidone; RTG, retigabine; RFM, rufinamide; STP, stiripentol; TGB, tiagabine; TPM, topiramate; VGB, vigabatrin; VPA, sodium valproate; ZNS, zonisamide
AED choice should be guided by its spectrum of action

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<th>Narrow-spectrum(^1,^2)</th>
<th>Broad-spectrum(^1,^2)</th>
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<td>Brivaracetam</td>
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Current antiepileptic drug targets

**Newer AEDs: Eslicarbazepine**

- Prodrug that is activated to eslicarbazepine (S-licarbazepine), major active metabolite of oxcarbazepine

- Adjunctive treatment or monotherapy for partial-onset seizures in adults

- Initial dose 400 mg PO once daily for 1 week, then increased to 800 mg PO once daily
  - 1,200 mg/day (maximum dose)

- Common adverse effects (ie, >10%) include dizziness, somnolence, nausea, headache, and diplopia
Newer AEDs: Eslicarbazepine

- Increased dose may be needed if coadministered with CYP enzyme-inducing AEDs (eg, carbamazepine, phenytoin, phenobarbital, primidone)

- Dosage reduction is recommended with moderate-to-severe renal impairment (200 mg/day initially for 2 weeks, then increase to 400 mg/day)
Newer AEDs: Eslicarbazepine

- Eslicarbazepine is licensed for adjunctive treatment in adults with focal seizures

- Its mechanism of action: blockade of voltage-gated sodium channel, a half-life of 20–24 hours, so it can be administered once a day

- It has a low potential for drug–drug interactions

- Efficacy with improvements over 50% ranged between 17–43%.
Newer AEDs: Eslicarbazepine

• Adverse effects were mild to moderate – commonly dizziness, somnolence, diplopia, abnormal co-ordination, blurred vision, vertigo.

• A study to evaluate eslicarbazepine, at doses between 400mg and 1200mg in stroke patients over a 2-year period, found that
  • Hyponatraemia developed in four out of 32 patients, and was symptomatic in three patients
  • Hyponatraemia symptoms can be subtle and delayed
Newer AEDs: Levetiracetam

• Synaptic vesicle protein 2A (SV2A), its function not been clearly defined

• SV2A important for availability of calcium-dependent neurotransmitter vesicles

• Lack of SV2A results in decreased action potential-dependent neurotransmission

• The role of SV2A in epilepsy confirmed by finding SV2A knockout mice develop a strong seizure phenotype a few weeks after birth
Newer AEDs: Levetiracetam

• Levetiracetam able to inhibit the synaptic vesicle protein 2a (SV2a)

• SV2a appears to be integral to the process of neurotransmitter exocytosis into synaptic cleft
  • Inhibition of this protein appears to result in broad-spectrum attenuation of excitatory activity

• Brivaracetam and seletracetam more potent inhibitors of this presynaptic protein and may provide an even broader spectrum of antiepileptic activity over levetiracetam
  • Brivaracetam may also inhibits fast inactivation of voltage-gated sodium channels
Newer AEDs: Levetiracetam

• Levetiracetam monotherapy outcomes from an epilepsy clinic were studied in 228 patients
  • 70.6% of whom had partial-onset seizures, 25.9% had idiopathic generalized epilepsies and 3.5% unclassied GTCS

• Seizure freedom was achieved in around half of patients on a median dose levetiracetam of 1000mg/day

• This was more likely to occur in those taking the drug as first monotherapy and in those with fewer than five pre-treatment seizures
Newer AEDs: Levetiracetam

- Levetiracetam monotherapy outcomes from an epilepsy clinic were studied in 228 patients
  - The drug was withdrawn in 16.2% of patients
  - 50% of these developed neuropsychiatric symptoms, *eg* depression, mood swings, irritability, depression
Newer AEDs: Levetiracetam

• **Advantage**
  • No drug interaction
  • Well tolerate and highly effective

• **Disadvantage**
  • Side effects: somnolence, asthenia, infection, dizziness, headache, emotional lability, depression

  • Behavioral problems particularly common in children and include agitation, hostility, anxiety, irritability, behavioral and psychotic changes and aggression

• **Life threatening**
  • Hepatic failure, hepatitis‡
Newer AEDs: Levetiracetam

• Clinical use
  • **FDA approved indications**:  
    – **Monotherapy and Adjunctive therapy for partial seizures in adults** (Class A)
  
  • Absence, myoclonic seizures
Newer AEDs: Brivaracetam

- Mechanism of action for brivaracetam (Briviact) unknown

- High and selective affinity for synaptic vesicle protein 2A (SV2A) in the brain,

- It is indicated as adjunctive therapy for partial-onset seizures in adults and children aged 16 y or older

- Dosage 50 mg PO BID, up to 100 mg BID (200 mg/day)
Newer AEDs: Lacosamide

• Lacosamide is unique functionalized amino acid specially synthesized for use AED

• It was approved in 2008 as adjunctive therapy for partial-onset seizures with or without secondary generalization, and restricted for specialist use in refractory epilepsy in people with epilepsy aged over 16 years

• Mechanism of action
  • Increase slow inactivation of voltage-gated sodium channels
  • Pharmacological response differs from sodium-channel blocking AEDs
  • Not interact with other AEDs, its anticonvulsant effect possibly antagonised by MAOIs and tricyclic-related antidepressants, mefloquine, antipsychotics
  • Risk of PR interval prolongation
Newer AEDs: Lacosamide

• A study comparing efficacy and safety of lacosamide in 118 paediatric and adult patients with uncontrolled epilepsy, showed

• Well tolerated in adults as in previous trials

• Adverse events occurring at a low frequency, related to the nervous and gastrointestinal systems, included dizziness, headache, nausea, diplopia and somnolence, with dyspepsia onset occurring during the titration period
Newer AEDs: Lacosamide

- The discontinuation rate due to side-effects was 8.5%

- A 50% seizure reduction was reported in 33–41% of patients receiving lacosamide 200mg–600mg a day

- There was a 50% responder rate in adults with refractory epilepsy.
Newer AEDs: Perampanel

- Perampanel showed inhibit AMPA-induced increases in intracellular calcium concentration
  - Agents that inhibit or decrease the AMPA receptor activity have potential to reduce excessive excitatory responses and confer neuroprotection

- Felbamate, topiramate has an inhibitory action on kainate receptors

- Phenobarbital has been reported to block AMPA receptors
Newer AEDs: Perampanel

• FDA (2012) approved [perampanel](#) as adjunctive treatment for partial-onset seizures (with or without secondary generalized seizures) and in June 2015 for primary generalized tonic-clonic seizures in adults or children aged 12 years or older

• Perampanel is a noncompetitive antagonist of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA).
Newer AEDs: Perampanel

• Advantage
  • New mechanism
  • Selective non-competitive antagonist of AMPA receptors
  • Once daily dosage
    • 2 mg PO q HS initially; increase by 2 mg/day increments in at least weekly, Dosage range: 4-12 mg/day

• Disadvantage
  • Dizziness and somnolence/sedation/fatigue most frequent dose-related adverse events
  • Neuropsychiatric events reported, aggression
  • Not recommended for use with severe hepatic or renal impairment or with hemodialysis.

• Life threatening
  • No
Newer AEDs: Perampanel

• Clinical usage
  • Partial-onset seizures with or without secondarily generalized seizures
  
  • Approved for treatment of primary generalized tonic-clonic seizures age >12 years
Do newer AEDs better compared to LVT as adjunctive treatments for uncontrolled focal epilepsy?

- Newer antiepileptic drugs (AEDs), such as Eslicarbazepine (ESL), Lacosamide (LAC), Perampanel (PER) and Brivaracetam (BRV), have been marketed as adjunctive treatments for partial-onset seizures.

- Many randomized controlled trials (RCTs) showed newer AEDs offer better seizure control than placebo when used as an adjunctive treatment for patients with partial-onset seizure.

- Due to the relatively small number of enrolled participants in individual studies and the lack of head-to-head comparisons between these newer drugs.
Do newer AEDs better compared to LVT as adjunctive treatments for uncontrolled focal epilepsy?

• it is still uncertain whether the claimed efficacy and safety of these latest AEDs can exceed those already been wildly prescribed

• Levetiracetam (LEV) is one of the most commonly used AEDs in clinical which have good efficacy and tolerability treat focal seizures
Meta-Analysis and Indirect Comparisons of Levetiracetam With Other Second-Generation Antiepileptic Drugs in Partial Epilepsy

Christian Otoul, Eng,* Celestina Arrigo, PhD,* Kenou van Rijckevoesel, MD,† and Jacqueline A. French, MD‡

Abstract: Few comparative clinical trials of newer antiepileptic drugs (AEDs) in patients with refractory partial epilepsy are available. Therefore, meta-analysis is a widely used and useful method for comparing them. Despite the limitations of indirect comparisons, and recognizing that these drugs were tested at different doses, such comparisons can be helpful to physicians making practical treatment decisions. The purposes of this study were to present newer meta-analysis results for add-on levetiracetam compared with placebo and to estimate its efficacy and tolerability compared with other new AEDs (gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate, and responder and/or withdrawal rate relative to several AEDs in patients with partial epilepsy with doses used in clinical trials. These meta-analyses give only short-term efficacy and safety data. Comparative clinical trials and long-term studies of these agents are needed to confirm these findings.

Key Words: meta-analysis, indirect comparison, refractory partial epilepsy, levetiracetam, antiepileptic drugs

(Clin Neuropharmacol 2005;28:72–78)
Levetiracetam having the highest odds ratio for response rate

- LEV was one of the AEDs with the lowest odds ratio for withdrawal


GBP: Gabapentin
LEV: Levetiracetam
LTG: Lamotrigine
OXC: Oxcarbazepine
TGB: Tiagabine
TPM: Topiramate
Long-term retention of lacosamide in a large cohort of people with medically refractory epilepsy: A single centre evaluation

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Retention of new AEDs (add-on) since 1999 at single tertiary care practice in UK

(largely patients with refractory focal epilepsy, all adults)

297 were followed prospectively for at least 2 years and 113 followed for at least 3 years

- Estimated retention of Lacosamide was 62% (95% CI 56-66) at one year
- 45% (95% CI 40-51) at two years
- 35% (95% CI 29-42) at three years

- 29% for LTG, 30% for TPM, 10% for GB, 58% for LEV

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<th>Significantly WORSE than</th>
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46,000 patients
195 RCTs
Assessed the no. of patients withdrawing because of AEs.

Discussion

• Three critical points may affect the results of this comparative analysis.
  • 1st: Dose of AEDs
    • Results of full-dose analysis show that BRV, GBP, GBP-ER, LEV, LTG, PER and ZNS were significantly better tolerated than one or more of the remaining AEDs.
    • ESL, LCM, OXC, PGB and showed a significantly worse tolerability compared to other drugs.
  • 2nd: Titration
    • The titration speed may have a relevant role for the appearance of dose-dependent adverse events.
  • 3rd: Several factors unrelated to the experimental drug such as
    • Tolerability of background treatments
    • Disease for which these drugs have been studied
    • Times and geographical areas in which studies

Discussion

• BRV, GBP, and LEV show the best tolerability profile while other AEDs are at higher risk for intolerable adverse effects.
Newer antiepileptic drugs compared to levetiracetam as adjunctive treatments for uncontrolled focal epilepsy: An indirect comparison

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ABSTRACT

Purpose: Newer antiepileptic drugs (AEDs), such as Eslicarbazepine (ESL), Lacosamide (LAC), Perampanel (PER) and Brivaracetam (BRV), have been marketed as adjunctive treatments for partial-onset seizures. Our aim was to compare the efficacy and tolerability of newer AEDs with Levetiracetam (LEV), when used as add-on treatments for uncontrolled focal epilepsy.

Method: We conducted an online database search on PubMed, Embase, Cochrane Online Library and ClinicalTrials.gov for all available randomized controlled trials (RCTs) investigating the therapeutic effects of newer AEDs or LEV vs placebo. Indirect comparisons for clinical efficacy and tolerability at different doses between the newer AEDs and LEV were then performed using Indirect Treatment Comparison (ITC) software.

Results: Twenty-four RCTs with a total of 8540 patients were included. Compared to LEV, ESL, LAC and BRV did not showed significant difference in efficacy at all dose level. PER showed lower 50% response rates and seizure-free rates at the highest effective recommended dosages. Treatment-emergent adverse events (TEAEs) and withdrawal rates due to adverse events (AEs) of LAC and PER were higher than LEV at the highest effective recommended dosages, and overall AE rates from ESL were higher than LEV.
Study design

- Because no published studies have compared newer AEDs with LEV directly

- By using indirect comparison for newer AEDs against LEV in patients with uncontrolled focal epilepsy
  - A common reference-based indirect comparison meta-analysis
  - By compare A with B indirectly, direct evidence should be provided by studies that compare A with C and B with C, respectively

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Study design

• Minimum effective recommended daily doses
  • ESL 800 mg
  • LCM 200 mg
  • PER 8 mg
  • BRV 50 mg
  • Versus LEV1,000 mg)

• Highest effective recommended daily doses
  • ESL 1200 mg
  • LCM 400 mg
  • PER 12 mg
  • BRV 200 mg
  • Versus LEV 3000 mg

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Study design

• Because of potential source of heterogeneity

• Two sensitivity analyses:
  • Removing the studies with small sample size
  • Including only RCTs where responder rates were calculated by comparing seizure frequency during baseline with during maintenance period

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Study design

• The twenty-five selected studies included a total of 8540 patients,
  • 4986 patients randomized to the newer AEDs
  • 948 to LEV treatment, and 2696 to placebo.

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Conventional meta-analysis per AED

• Most of newer AEDs showed significant higher rate in 50% responder rate and seizure-free rate compared to placebo at all dose level

• Only seizure free rates at minimum effective daily doses for LAC and BRV, and highest effective recommended dose for PER did not reach statistical significance over placebo

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Conventional meta-analysis per AED

• The RDs of tolerability in newer AEDs or LEV treatment vs. placebo patients
  
  • No significant differences in TEAEs, withdrawal rates due to AEs and SAEs in all dose levels compared to placebo for BRV and LEV
  
  • For ESL, statistically significant differences in TEAEs and withdrawal rates due to AEs were found in all dose levels compared to placebo

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Conventional meta-analysis per AED

• The RDs of tolerability in newer AEDs or LEV treatment vs. placebo patients

  • LAC showed higher risk of TEAEs, withdrawal rates due to AEs and SAEs at the highest effective recommended dose

  • PER also had higher risk of TEAEs and withdrawal rates due to AEs at the highest effective recommended daily dosages and at all doses combined

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50% responder rates and Seizure freedom

• 50% responder rates of patients with uncontrolled focal epilepsy were
  • Significantly lower for PER 12 mg compared to LEV 3000 mg [RD 0.12, 95% CI (0.223, 0.017)]

• Seizure freedom
  • significantly lower for PER compared to LEV at the highest effective recommended daily dosages [RD 0.05, 95% CI (0.093, 0.007)] and at all doses combined [RD 0.03, 95% CI (0.055, 0.005)]

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Treatment-emergent adverse events

• TEAE significantly higher than LEV at highest effective recommended daily dosages
  • ESL
  • LAC
  • PER

• There was a significantly higher risk on TEAEs compared to LEV at all doses combined ESL
  • PER

• Higher TEAEs compared to LEV at minimum effective recommended daily doses
  • ESL

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Withdrawal rates due to AEs

- The indirect comparison demonstrated that there were significantly higher risks of AEs compared to LEV at the highest effective recommended daily dosages for those taking
  - ESL
  - LAC
  - PER

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Risk of experiencing SAEs

- Risk of experiencing SAEs compared with to LEV did not differ from (at the minimum, the highest effective recommended daily dosages or at all doses combined)
  - ESL
  - LAC
  - PER
  - BRV

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Discussion

• This study compared the efficacy and tolerability between newer AEDs and LEV when used as add-on treatment in patients with uncontrolled focal epilepsy by evaluating twenty-five randomized placebo-controlled studies

• All patients were adults with focal epilepsy uncontrolled by one or more AEDs

• None of studies had high risk of selection bias, performance bias, or detection bias. Therefore, included studies were overall clinically and methodologically homogeneous

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Discussion

• Comparing to LEV, PER was less efficacious both in terms of 50% responder rates and rates of seizure freedom at the highest effective recommended daily dosages.

• However, ESL, LAC and BRV were not inferior to LEV in either 50% responder rates or seizure freedom rates at all dose levels.

• There was a trend toward better efficacy for LEV versus any of the newer AEDs because the RDs at all dose levels were >0.

Discussion

• The overall rates of adverse effect from ESL were disappointingly higher than that of LEV

• Also, a possible worse tolerability profile of high dose LAC and PER compared to high dose LEV

• BRV exhibited a similar tolerability to LEV

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Discussion

• As is known AEs (ataxia, dizziness, etc) are frequently associated with AEDs acting on voltage-gated sodium channels
  • such as ESL and LAC, which may appear at high doses or with a short titration.

• However, with its novel mechanism, AEs of LEV might not be that dose-dependent.

• Because of short observation periods, it not reveal long-term AEs.

• Also, the specific AEs, such as anxiety, depression, etc, was not compared, which might be different between the newer AEDs and LEV

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Discussion

• Even though large scale of investment has been put into the development of new AEDs, outcome was disappointing

• New AEDs did not show significant superiority over LEV on efficacy.

• On the other hand, adverse events was higher than LEV

• On a larger scale, latest study implied proportion of drug resistant epilepsy patients in all epilepsy population did not change significantly

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Take home message

• This meta-analysis suggested that among the newer AEDs, ESL, LAC and BRV were not inferior to LEV in efficacy
  • PER may be less efficacious at the highest effective recommended daily dosages compared to LEV

• A possible worse tolerability profile of ESL, LAC and PER compared to LEV at high dose was found

• BRV exhibited a similar tolerability to LEV

L.-Zhu., et.al. Newer antiepileptic drugs compared to levetiracetam as adjunctive treatments for uncontrolled focal epilepsy: An indirect comparison. Seizure 2017; 51: 121-132
Efficacy and Tolerability of Second and Third Generation Anti-epileptic Drugs in Refractory Epilepsy: A Network Meta-Analysis

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This study was proposed to compare the relative efficacy and tolerability of the second and third generation AEDs for refractory epilepsy. The 50% responder rate (RR) was selected as the efficacy outcome whereas the incidence of dizziness and somnolence were considered to evaluate the tolerability of AEDs. Odds ratio (OR) and their 95% credible interval (CrI) were obtained using a consistency model and surface under the cumulative ranking curve (SUCRA) value was calculated to rank AEDs. Topiramate appeared to be significantly more effective than placebo, eslicarbazepine acetate, perampanel, pregabalin, zonisamide, gabapentin and lamotrigine with respect to the 50% RR (all OR > 1). Patients who were managed by eslicarbazepine acetate, perampanel, oxcarbazepine, topiramate and pregabalin were more likely to suffer from dizziness compared to those who receive...
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• To compare the relative efficacy and tolerability of the second and third generation AEDs for refractory epilepsy

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- Topiramate appeared to be significantly more effective (with respect to the 50% RR (all OR > 1) than
  - Placebo
  - Eslicarbazepine acetate
  - Perampanel
  - Pregabalin
  - Zonisamide
  - Gabapentin
  - Lamotrigine

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• Patients who were managed by eslicarbazepine acetate, perampanel, oxcarbazepine, topiramate and pregabalin were more likely to suffer from dizziness compared to those who receive placebo (all OR > 1)

• Perampanel, topiramate and pregabalin were related to elevated risks of somnolence compared to placebo (all OR > 1).

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• Moreover, topiramate ranked highest with respect to 50% RR (SUCRA = 0.968) whereas levetiracetam appeared to have balanced efficacy and tolerability (SUCRA = 0.769, 0.743, 0.604 and 0.659)

• In conclusion, topiramate was the most efficacious AED, while levetiracetam was able to provide patients with balanced efficacy and tolerability

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Evaluate the Efficacy and Safety of Anti-Epileptic Medications for Partial Seizures of Epilepsy: A Network Meta-Analysis

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ABSTRACT

Epilepsy is a brain and neurological disorder with high prevalence. It was reported that more than 70% of epileptic seizures were controlled by anti-epileptic medications, whereas the lack of evidence with respect to head-to-head comparisons motivated researchers to seek alternative approaches that are able to provide deep insights into the profile of anti-epileptic medications. In this study, we performed a network meta-analysis (NMA) to evaluate the efficacy and safety of anti-epileptic medications for partial seizures of epilepsy. Publications were retrieved from PubMed, Embase, and Cochrane Library. Then, studies were screened and selected based on the inclusion criteria. Data were extracted and a NMA was performed to combine both direct and indirect evidence. Surface under the cumulative ranking curve (SUCRA) was obtained for ranking purposes. Consistency between direct and indirect evidence was assessed by using the node-splitting method. Seventeen anti-epileptic medications from 90 publications were enrolled. Fifty percent responder and state of seizure freedom were studied as outcomes for efficacy; treatment emergent adverse effect (TEAE), including dizziness, somnolence, headache, fatigue, and nausea were evaluated as safety outcomes. Topiramate, levetiracetam, pregabalin, and oxcarbazepine were recommended for their relatively high efficacy and low-risk of adverse events for partial seizures. Rufinamide was the least preferable medication due to its low efficacy and high-risk of adverse effects. J. Cell. Biochem. 118: 2850–2864, 2017. © 2017 Wiley Periodicals, Inc.
Study design

- Fifty percent responder and state of seizure freedom were studied as outcomes for efficacy; treatment emergent adverse effect (TEAE), including dizziness, somnolence, headache, fatigue, and nausea were evaluated as safety outcomes.
NMA analysis AEDs

- In this NMA, LEV was proved to be effective with respect to both 50% responder and seizures freedom and exhibited a relative low risk of any TEAE and headaches.
  - However, nausea seemed to be more likely to occur in LEV-treated patients.

- TPM was effective with high ranks in both the 50% responder and seizure freedom.
  - Higher risk of somnolence and fatigue in patients taking TPM compared with other medications.

- PGB proved to be effective with respect to the 50% responder; it may not be as effective as TPM and OXB with respect to seizure freedom
  - PGB exhibited a relative low-risk of headache and nausea which were two serious adverse effects that might cause withdrawal from medications
  - Dizziness, somnolence, and fatigue more likely to occur in patients taking PGB than other drugs