Antiseizure Medication Combinations in the Treatment of Drug-resistant Epilepsy

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Disclosures

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Learning objectives

- Review evidence for combination therapy versus alternative monotherapy after failure of the first ASM
- Review ASM mechanisms of action, pharmacodynamic interactions, and pharmacokinetic interactions
- Discuss evidence favoring specific ASM combinations

Patterns of ASM use over time

- In the 1970s and early 1980s, polytherapy was the rule, particularly for drug resistant patients
- Phenobarbital-phenytoin combination was often the initial treatment and the two ASMs were even combined in a single pill for convenience
- With the introduction of additional ASMs, primidone, carbamazepine, clonazepam, and valproic acid, combination therapies were associated with unfavorable interactions and toxic adverse effects
- The term "polypharmacy" was introduced, with negative connotations
- Studies reported cognitive benefits of converting patients to monotherapy, usually without worsening seizure control

Patterns of ASM use over time

- With the introduction of many new ASMs, most of which FDA-approved only for adjunctive therapy, the notion of rational polytherapy was introduced, evaluating harmonious or synergistic ASM combinations
- In comparison with classical ASMs, some newer ASMs were less sedating, had improved tolerability profile and lower potential for pharmacokinetic interactions, making them suitable adjunctive agents
- It was proposed that excessive ASM load may have played a role in poor tolerability, and low doses of ASMs in combination may be better tolerated
- Monotherapy continues to be the standard for initial therapy

Choosing the first ASM

- Efficacy against seizure type
  - Mechanism of action usually not relevant for newly diagnosed focal epilepsy (except ethosuximide)
  - For generalized epilepsy, ASMs with multiple mechanisms have broad spectrum. ASMs that act on T-calcium channel are effective against absence
- Individual considerations (co-morbidity, urgency of action- need for slow titration, cognitive function, gender, age, co-medication, etc...)
- Tolerability and safety

After failure of first ASM, should it be new monotherapy or add-on? Kwan and Brodie, Seizure 2000

- Prospective study of 248 patients who failed first ASM
  - When failure was due to lack of efficacy, either ASM substitution or combination (add-on) was undertaken.
  - Patients were considered seizure-free if they had no seizures for ≥ 1 yr
- **Similar sz-free rates (substitution vs. add-on: 17% vs. 26%) and incidence of intolerable side effects (substitution vs. add-on: 26% vs. 12%)**
- More patients became seizure-free when the combination involved a sodium channel blocker and a drug with multiple mechanisms of action* (36%) compared to other combinations (7%; p=0.05) *VPA, TPM , GBP
- 26% of 42 patients who received add-on as soon as the first tolerated ASM proved to be ineffective became seizure-free vs 0/11 patients who received add-on treatment after a second drug had also failed (p=0.05).

Updated Glasgow cohort

Hakeem et al, Epilepsia 2022

- Overall, 21% (104/498) of the patients achieved seizure freedom on the second ASM regimen, which was less than half of the seizure-free rate on the initial ASM monotherapy (45%, $p < .001$).
- Second ASM regimen prescribed as combination therapy increased from 46% in 1985–1994 to 63% in 1995–2004 and 78% in 2005–2015.
- Similar seizure-free rates were observed in the 152 patients switched to substitution monotherapy ($n = 30$, 20%) and the 346 patients treated with combination therapy ($n = 74$, 21%, $p = .68$)
- **Combination of sodium channel blocker and levetiracetam had a better chance to achieve seizure freedom** compared to the pooled other combinations (RR = 2.12, 95% CI: 1.11–4.03, $p = .023$)

Should it be new monotherapy or add-on?

Beghi et al, Epi Res 2003

- Multicenter, randomized, controlled open label trial in patients with focal epilepsy failing a single drug
- Adjunctive therapy vs alternative monotherapy
- ASM choice & dose adjustments by physician judgment
- FU for 12 months or until withdrawal from allocated treatment.
- 157 pts- 76 alternative monotherapy, 81 to adjunctive therapy
- **12-month probability of remaining on assigned Rx**
  - **55% in patients randomized to alternative monotherapy**
  - **65% in those randomized to adjunctive therapy ($P = 0.74$)**
- **12-month probability of remaining seizure-free: 14 and 16% (NS)**
- **Adverse effects were similar in the two groups**

Scenarios favoring substitution monotherapy

Abou-Khalil, CNS Drugs 2017

- First ASM not tolerated
- First ASM totally ineffective
- Elderly patients
- Women of child-bearing potential contemplating pregnancy
- Patients with compliance challenges
- Patients limited by financial considerations

Scenarios favoring add-on therapy

Abou-Khalil, CNS Drugs 2017

- First ASM well-tolerated and partially effective
- First ASM effective with complete seizure control, but only at doses that are not well tolerated; well-tolerated at lower doses
- +/- add-on ASM considered not-well tested in monotherapy

List of seizure medications

Old ASMs (up to 1978)

- Phenobarbital
- Phenytoin (Dilantin, Phenytek)
- Primidone (Mysoline)
- Carbamazepine (Tegretol, Carbatrol)
- Valproate (Depakote)
- Clonazepam (Klonopin)
- Methsuximide (Celontin)
- Ethosuximide (Zarontin)

New ASMs (1993-2005)

- Felbamate (Felbatol)
- Gabapentin (Neurontin)
- Lamotrigine (Lamictal)
- Topiramate (Topamax)
- Tiagabine (Gabitril)
- Levetiracetam (Keppra)
- Oxcarbazepine (Trileptal)
- Zonisamide (Zonegran)
- Pregabalin (Lyrica)

Newest ASMs (since 2008)

- Lacosamide (Vimpat)
- Rufinamide (Banzel)
- Vigabatrin (Sabril)
- Clobazam (Onfi)
- Retigabine (Potiga)
- Perampanel (Fycompa)
- Eslicarbazepine (Aptiom)
- Brivaracetam (Briviact)
- Cannabidiol (Epidiolex)
- Cenobamate (Xcopri)
- Stitipentol (Diacomit)
- Fenfluramine (Fintepla)

Choosing the add-on ASM

- Efficacy against seizure type
- Individual considerations (co-morbidity, urgency of action-need for slow titration, cognitive function, gender, age, co-medication, etc...)
- Tolerability and safety
- **Pharmacokinetic interactions**
- **Pharmacodynamic interactions (related to shared mechanism of action)**
- **Mechanism of action**

Pharmacokinetic interactions

- Are associated with change in serum concentration
- May occur at the level of drug absorption, distribution, metabolism, excretion
- Most often related to enzyme induction or inhibition

Enzyme induction

- A slow process that builds up gradually after addition of an inducer
- Enzyme-inducing ASMs include phenobarbital, primidone, phenytoin, carbamazepine. These ASMs induce multiple p450 enzymes, increasing the clearance of drugs metabolized by these enzymes
- Some newer ASMs are selective enzyme inducers. For example, oxcarbazepine and eslicarbazepine are weak inducers of CYP3A4, which metabolizes estrogen

Enzyme inhibition

- Takes place rapidly, with buildup of the drug whose metabolism is inhibited
- Valproate inhibits metabolism of phenobarbital, ethosuximide, carbamazepine epoxide (active carbamazepine metabolite), lamotrigine, and rufinamide, resulting in increased concentrations of these compounds
- Felbamate inhibits the metabolism of phenytoin, valproate, carbamazepine epoxide, and N-desmethylclobazam
- Cenobamate inhibits metabolism of phenytoin, phenobarbital, and N-desmethylclobazam
- New ASMs are occasionally selective weak inhibitors. For example, oxcarbazepine and topiramate are weak inhibitors of CYP2C19, which metabolizes phenytoin, and may cause an increase in phenytoin level

Pharmacokinetic interaction via protein binding

- Highly protein-bound ASMs may displace each other from serum proteins, with resulting increase in protein-free fractions
- The protein-free fraction may also be increased in low protein states, hepatic and renal failure, pregnancy, and old age
- The protein-free fraction is the most clinically relevant for both toxicity and efficacy
- The change in protein binding is of clinical relevance when dosing decisions are made based on total serum concentration

Pharmacokinetic interactions and rational polytherapy

- Unfavorable interactions need to be avoided
  - **Enzyme inducers** may make adjunctive ASM less effective, requiring higher dose
  - Some combinations cause increased levels of certain toxic metabolites (for example CBZ epoxide in CBZ-VPA or CBZ-FBM combination; toxic VPA metabolites with concomitant enzyme inducers)
- Inhibitors allow lower doses of adjunctive affected ASM (ex lower LTG dose with VPA)

Pharmacodynamic interactions

- Not associated with a change in concentration
- Related to mechanism of action
- Combining two ASMs with same mechanism may cause adverse experiences even though the levels are in the "therapeutic" range
- Combining two ASMs with different mechanisms reduces chance of adverse pharmacodynamic interaction
- Do different mechanisms predict better efficacy?

ASM main mechanisms of action

- **Na channel blocking**
- **Enhancing GABA**
- Glutamate receptor antagonism
- Blocking high voltage activated calcium channels
- Blocking T- calcium channels
- Binding Alpha-2-delta subunit of voltage-activated calcium channels
- Binding synaptic vesicle protein SV2A
- K-channel opening
- Modulation of intracellular Ca
- Enhancing serotonin

Na channel blocking

- Enhancement of fast inactivated state- blocking of sustained repetitive firing:
  - Phenytoin, carbamazepine, oxcarbazepine, lamotrigine, rufinamide, eslicarbazepine
- Selective enhancement of slow inactivation of voltage-gated sodium channels
  - Lacosamide
- Multiple mechanisms, including effect on sodium channels
  - Valproate, felbamate, topiramate, zonisamide, cenobamate

Enhancing GABA

- **Irreversible inhibition of GABA transaminase: vigabatrin**
- **Inhibition of GABA reuptake at the synapse: tiagabine**
- **Prolongation of GABA-mediated chloride channel openings: phenobarbital**
- **Increased frequency of GABA-mediated chloride channel openings: benzodiazepines**, topiramate (different binding site- also increases GABA levels in the brain by MRS)
- Enhancing GABA transmission in specific circuits: valproate
- Enhancing GABA-elicited Cl^- currents: felbamate
- Positive allosteric modulation of GABA-A receptors: cenobamate, cannabidiol
- Several ASMs are associated with acute elevation of brain GABA by MRS after single doses: 70% for topiramate, 48% with gabapentin.

Effectiveness of ASM Combinations for Partial-Onset Seizures Based on MOA

Margolis et al, JAMA Neurol 2014

- Adults with concomitant use of 2 different ASMs and a recent partial-onset seizure diagnosis were studied, using the Truven Health MarketScan Commercial Claims Database (96 million covered lives from 7/1/04 to 3/31/11)
- ASMs were categorized by MOA: sodium channel blockers (SC), GABA analogs (G), SV2A binding (SV2), and multiple mechanisms (M)
- Treatment persistence was measured from the start of ASM combination therapy until the end of the combination
- Health care resource use was measured during the combination treatment duration

Effectiveness of ASM Combinations for Partial-Onset Seizures Based on MOA

Margolis et al, JAMA Neurol 2014

- 8615 selected patients
- Most common combinations were SC+SV2 (26.3%), SC+M (21.5%), G+SC (19.0%), SC+SC (13.9%), G+M (8.6%), G+SV2 (7.5%), G+G (3.3%)
- **Combinations with same MOA (G+G and SC+SC) had the shortest persistence** and greater hazard of discontinuation compared with different-MOA combinations- **SC+SV2 had the greatest persistence**
- Patients with different-MOA G combinations had a lower risk for inpatient admission compared with G+G combinations
- Patients with different-MOA SC combinations had significantly lower risks for ED visits compared with SC+SC combinations

THERAPEUTIC ADVANCES in
Neurological Disorders

Original Research

Optimizing treatment persistence in epilepsy: a comparative analysis of combined antiseizure medications with different mechanisms of action

Ther Adv Neurol Disord

2023, Vol. 16: 1–13

DOI: 10.1177/17562864231207161

Chun-Wei Chang, Wei-En Johnny Tseng, Wey-Ran Lin, Po-Chuan Ko, Chun-Jing Liu and Siew-Na Lim

3033 patients with epilepsy in Taiwan

ASM combinations with different MoAs had significantly longer treatment persistence than ASMs with similar MoAs ($p<0.001$).

The SC + SV2 combination had the longest treatment persistence

Animal studies of ASM combinations- isobolography

Czuczwar, 2009; Stafstrom, 2010, Verrotti 2020

- Combinations can be additive, antagonistic (infra-additive), or synergistic (supra-additive), for efficacy and adverse effects
- The most favorable combinations have supra-additive efficacy and infra-additive neurotoxicity
- Combining drugs with similar mechanism such as two classical sodium channel blocking drugs results in infra-additive or additive efficacy and supra-additive or additive toxicity

Evidence supporting efficacy of specific combinations in animal studies

Czuczwar, 2009; Stafstrom, 2010, Verrotti 2020

- The most favorable combinations involve drugs with different MOA such as sodium channel blocking + multiple mechanisms
- Animal models using isobolography support several combinations as synergistic

- **VPA+LTG**
- GPN+VGB
- OXC+LEV
- OXC+GPN
- OXC+TGB
- LEV+TPM
- LEV+CBZ
- LTG+TPM
- TGB+GPN
- VPA+PHT
- VPA+ESX
- VPA+GPN
- VPA+TPM
- VPA+VGB
- CBZ+GPN
- CBZ+TPM
- OXC+TPM
- PHB+TPM
- TPM+FBM
- **CBD+CLB** Rana 2023

Combinations showing synergy in clinical studies

Park, J Epilepsy Research 2019

Drug combination	Level of evidence
Valproate and lamotrigine	+++
Valproate and ethosuximide	++
Lamotrigine and topiramate	+
Lacosamide and levetiracetam	++
Lamotrigine and levetiracetam	++
Valproate and levetiracetam	+

Combinations containing enzyme-inducing drugs were excluded.
+++, from controlled trials; ++, from case series or observational studies; +, case reports.

VPA-LTG synergy

Brodie and Yuen, 1997

- 347 patients not fully controlled with VPA (117), CBZ (129), PHT (92) or PB (9) monotherapy were recruited into a LTG substitution study
- LTG was initially added to the baseline ASM, followed by an attempt to withdraw the original ASM, then 12 weeks of LTG monotherapy
- The addition of LTG to VPA (64% responders) produced a significantly better response ($p<0.001$) than adding it to CBZ (41% responders) or PHT (38% responders)
- Effect was seen for focal (VPA, 57%; CBZ, 39%; PHT, 39%; $P<0.02$) as well as 1ary tonic-clonic seizures (VPA, 70%; CBZ, 53%; PHT, 50%; NS)

VPA-LTG synergy

Pisani et al, Epilepsia 1999

- After a 3-month prospective baseline, 20 adults with refractory complex partial seizures not exposed previously to VPA and LTG were scheduled to receive three consecutive add-on treatments with VPA, LTG, or VPA-LTG combination, according to an open, response-conditional, crossover design
- Each period consisted of a 6- to 12-week dose optimization followed by 3-month evaluation at stabilized serum drug levels. Only patients not responding to one phase proceeded to the next

VPA-LTG synergy Pisani et al, Epilepsia 1999

- A >50% reduction in seizure frequency was observed in 3/20 pts (15%) given VPA and in 4/17 (23.5%) given LTG. Of the remaining 13 patients, 8 (61%) were responders with LTG-VPA combination
  - 4 (40.5%) became seizure free, and an additional 4 (40.5%) experienced 62-78% seizure reduction
- In patients responding to combination therapy, optimized dosages and peak serum levels of both VPA and LTG were lower than during separate administration

Comparative efficacy of combination drug therapy in refractory epilepsy

Poolos et al, Neurology 2012

- Analyzed treatment records from 148 developmentally disabled adults with refractory epilepsy cared for in 2 state-run institutions
- Monthly convulsive seizures and ASM regimen charted over 30 yrs
- Studied effect of 8 commonly used ASMs (monotherapy or combinations of 2-3 ASMs) on seizure frequency
- ASMs studied in order of use, starting with most commonly used: LTG, VPA, CBZ, PHT, TPM, LEV, GBP, ZNS

Comparative efficacy of combination drug therapy in refractory epilepsy

Poolos et al, Neurology 2012

- Used data where there was at least 4 months of exposure to a given ASM combination
- Calculated average seizure frequency per month during the entire time of exposure to each ASM combination
- Comparisons of efficacy made using within-patient ratios of seizure frequency (to all other combinations or to specific combination)

Comparative efficacy of combination drug therapy in refractory epilepsy

Poolos et al, Neurology 2012

- Dual therapy provided better efficacy than monotherapy
- Combinations of 3 ASMs had no advantage over 2 ASMs
- The combination of lamotrigine and valproate provided significantly better efficacy than other combinations ($p=3x10^{-6}$), particularly in patients with focal epileptiform abnormalities- not explained by pharmacokinetic interaction

Other combinations with clinical evidence of synergism- first and second generation Rxs

- VPA- ESX (ethosuximide)- Rowan et al, Arch Neurol 1983
  - 5 patients resistant to VPA and to ESX became seizure-free with combination therapy
- LTG-LEV (levetiracetam) combination- Kinirons et al, Seizure 2006
  - 344 drug-resistant patients treated with LEV- LTG was used more often in seizure-free patients and responders than in non-responders ($p=0.003$)
- VNS-Ketogenic diet- Abdelmoity, Epilepsia Open 2021, Kossoff, Epilepsia 2007

How about newer generation ASMs?

Evidence for or against certain combinations

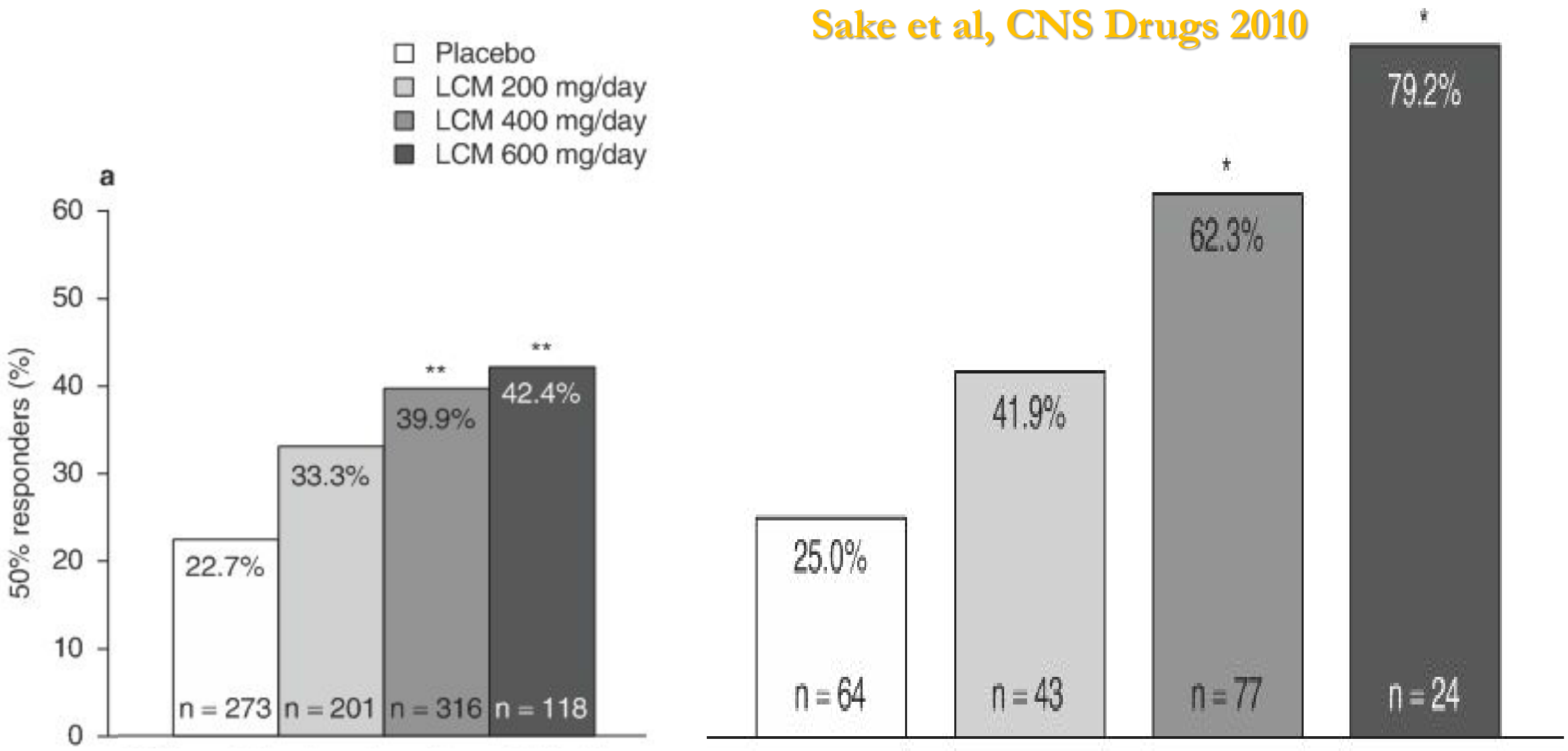
Lacosamide (LCM) combinations

Sake et al, CNS Drugs 2010

- Post hoc exploratory analyses performed on pooled clinical trial data (1308 patients)
- Patients grouped by concomitant ASMs including or not a 'traditional' Na channel-blocking ASM (CBZ, LTG, OXC, PHT)
- 82% were using at least one concomitant 'traditional' Na channel-blocking ASM
- **Efficacy was more pronounced, and adverse experiences were less frequent in the subgroup without concomitant traditional Na channel blocking ASM**

LCM pooled trial data- 50% Responder rate

Sake et al, CNS Drugs 2010



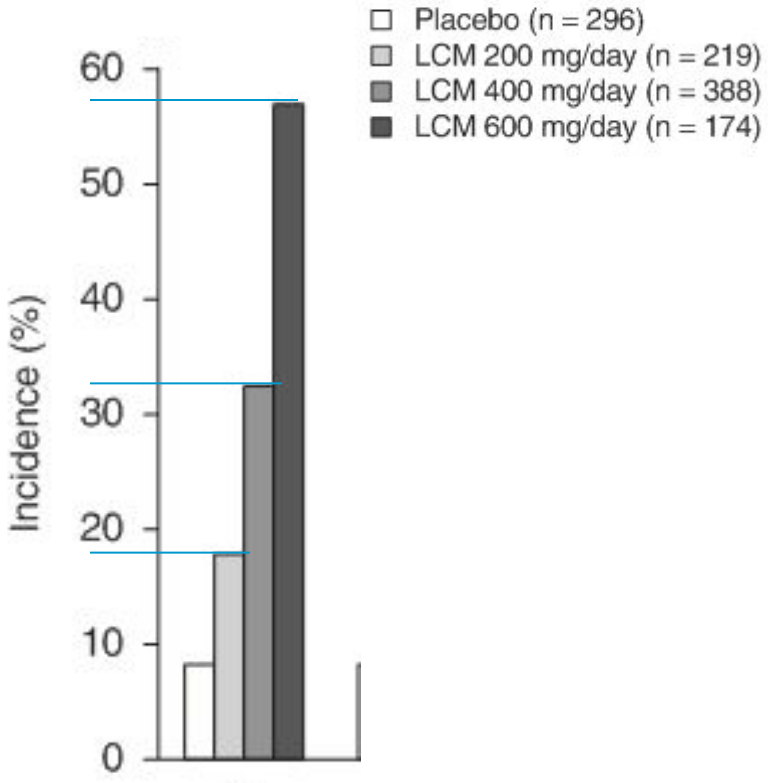
With traditional Na channel blocking ASMs

No Na channel blocking ASMs

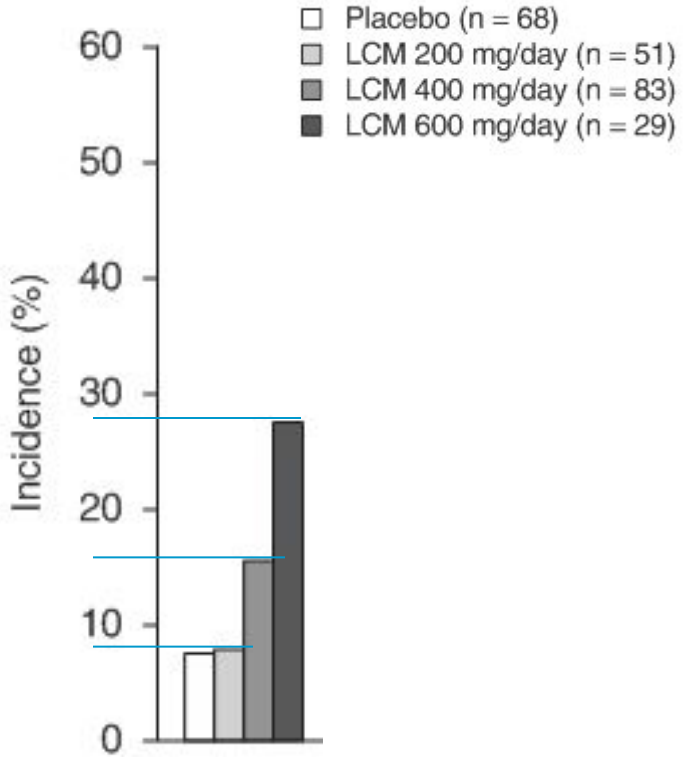
LCM pooled trial data- Dizziness as an adverse experience

Sake et al, CNS Drugs 2010

Traditional Na channel blocking ASMs



No Na channel blocking ASMs



Eslicarbazepine adjunctive therapy-concomitant ASM

Biton at al, 2017

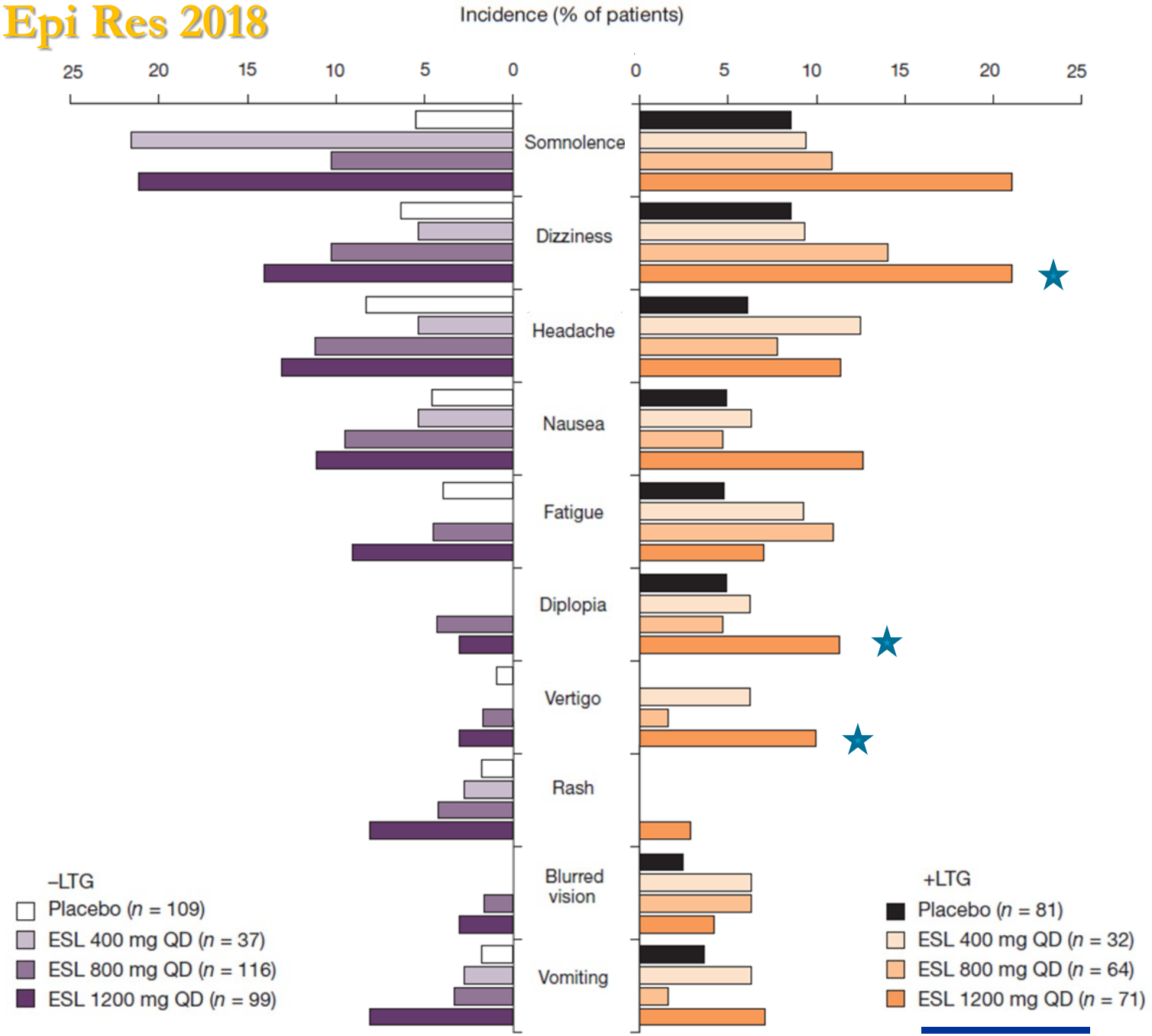
- Patients taking concomitant CBZ had less marked improvements in efficacy outcomes than those taking other concomitant ASMs, but these differences in outcomes were not significant
- Patients taking concomitant CBZ had higher placebo-adjusted rates of dizziness, diplopia, vomiting, and nausea (ESL 800 and 1200 mg groups) than those not taking CBZ

Eslicarbazepine +/- LTG

Abou-Khalil et al, Epi Res 2018

- Post-hoc analysis of data pooled from three Phase III clinical studies of ESL, to evaluate the impact of concomitant LTG use (in patients not taking CBZ or PHT) on incidence of AEs during adjunctive ESL treatment
- Overall placebo-adjusted incidence of TEAEs higher in the LTG group (+LTG: 16%, –LTG: 10%; in 1200 mg group 25% vs 17%). Effect was less prominent than with concomitant CBZ
- In the ESL 1200 mg treatment arm, some specific TEAEs had a higher incidence in the +LTG subgroup than the –LTG subgroup, but no differences were statistically significant (dizziness: +LTG 21%, -LTG 14%, p=0.232; diplopia: +LTG 11%, -LTG 3%, p=0.054; vertigo: +LTG 10%, -LTG 3%, p=0.096)

Abou-Khalil et al, Epi Res 2018



Perampanel Combinations

Kwan et al, Epilepsy Research 2015

- Data pooled from three phase III trials of adjunctive perampanel in patients with refractory partial-onset seizures
- Concomitant ASMs were categorized according to whether or not they were enzyme-inducing ASMs (EIASMs) or sodium channel blockers (SCBs)
- Post hoc analyses assessed the impact of co-administration of non-EIASM SCBs and the overall number of concomitant ASMs on changes in seizure frequency, 50% responder rates, rates of treatment-emergent adverse events (TEAEs), and rates of discontinuation due to TEAEs, in patients randomized to receive daily placebo or perampanel 2, 4, 8, or 12 mg

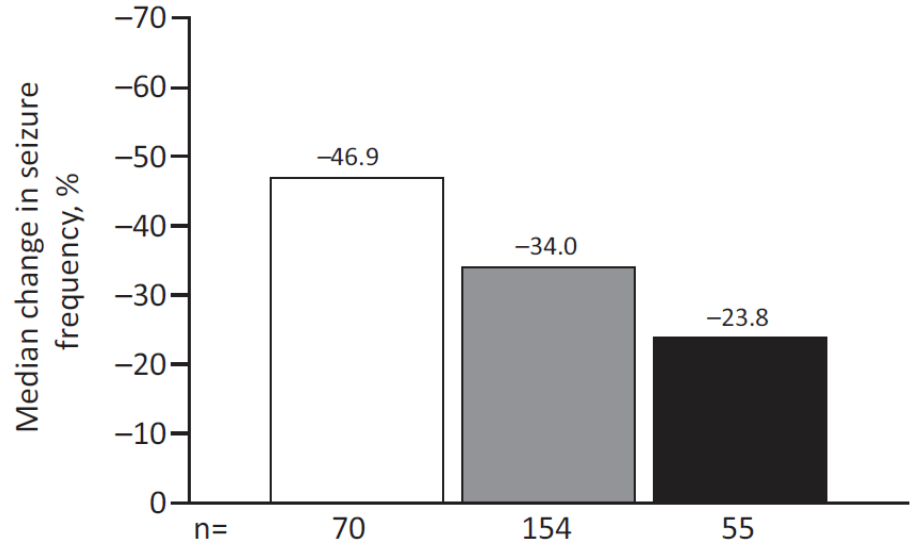
Perampanel Combinations

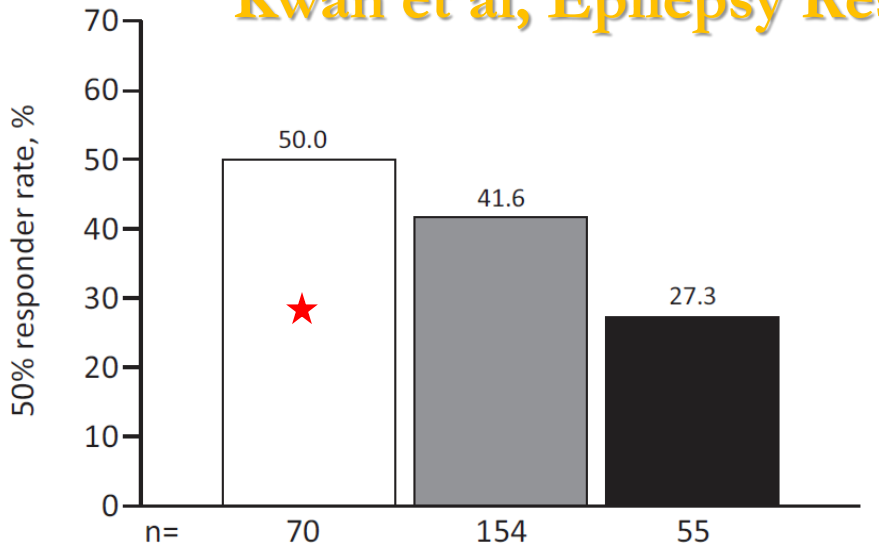
Kwan et al, Epilepsy Research 2015

- 1480 randomized and treated patients
- Most were receiving ≥ 2 concomitant ASMs (n = 1273, 86.0%), ≥1 EIASMs (n = 1083, 73.2%), and/or ≥1 SCBs (n = 1203, 81.3%) at baseline
- **Efficacy was reduced by enzyme inducing ASMs (EIASM)**
- Magnitude of seizure reduction unaffected by the presence of non-EIASM SCBs, but lower in the presence of multiple ASMs
- Frequency of TEAEs did not appear to be affected by the presence of non-EIASM SCBs or multiple ASMs

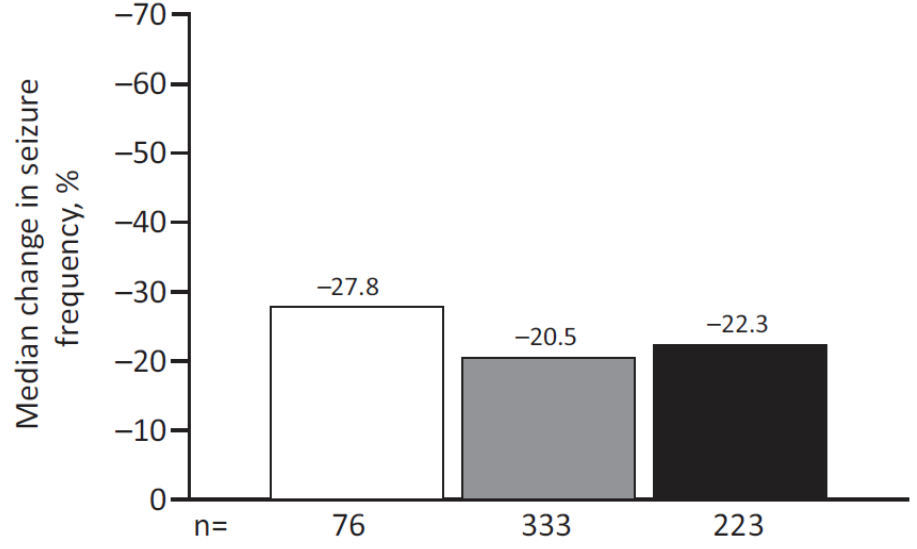
Kwan et al, Epilepsy Research 2015

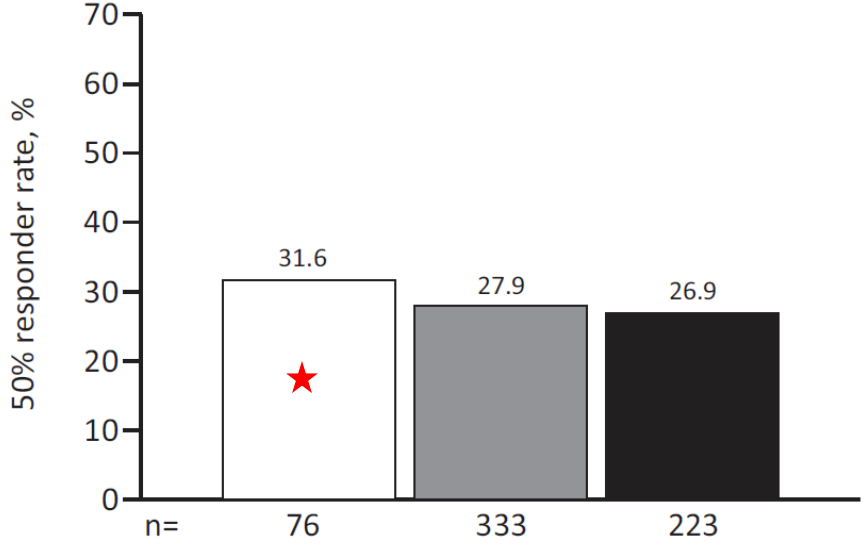
A. No EIAEDs





B. One EIAED





1-AED regimen 2-AED regimen 3-AED regimen

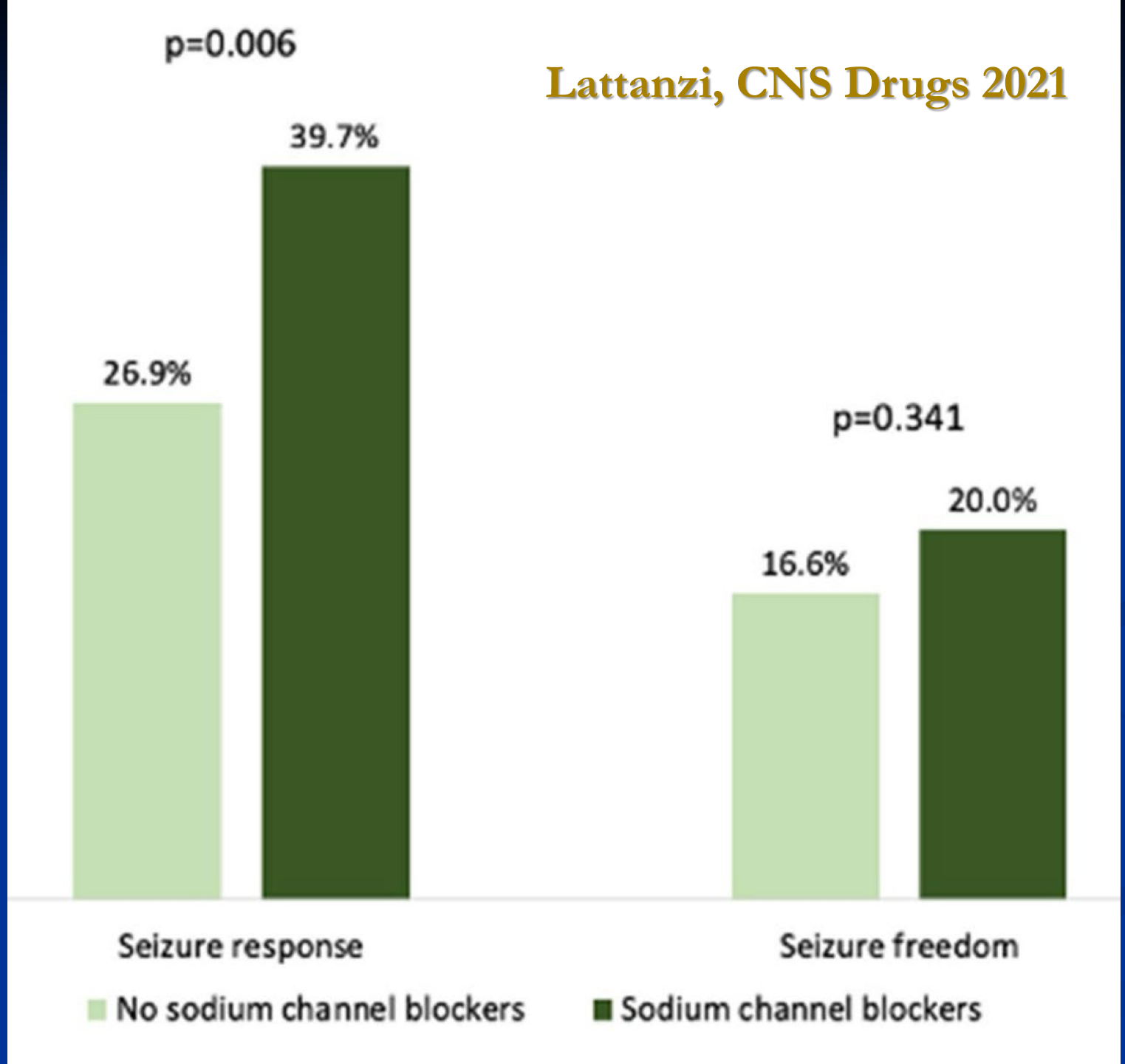
Brivaracetam Combinations

- Brivaracetam approximately doubles carbamazepine epoxide plasma concentration, consistent with a dose-dependent and reversible inhibition of epoxide hydrolase **Stockis, Epi Rs 2016**
- **Brivaracetam is not effective in patients taking levetiracetam**
- No clear difference in efficacy for combination with lamotrigine vs topiramate **Benbadis, Epilepsy & Behavior 2018**
- **More effective in the presence versus absence of a sodium channel blocker** **Lattanzi, CNS Drugs 2021**

Brivaracetam Combinations

Lattanzi, CNS Drugs 2021

- Multicenter Italian study of adjunctive BRV in 1029 adult patients with focal epilepsy in the context of real-world clinical practice
- At 12 m 16.4% were seizure-free and 37.2% were responders
- Rate of seizure freedom: 22.3% in LEV-naive pts, 7.1% in pts with prior LEV use and discontinuation due to insufficient efficacy, and 31.2% in pts with prior LEV use and discontinuation due to AEs ($p < 0.001$)
- **Responder rate (39.7% vs 26.9%; p= 0.006) and rate of seizure freedom (20.0% vs. 16.6%; p = 0.341) were higher in patients receiving SCBs than those not receiving SCBs**
- **AEs were less common in patients treated with concomitant SCBs than those not treated with SCBs (28.9% vs. 39.8%; p = 0.017)**



Add-on brivaracetam efficacy according to concomitant use of sodium channel blockers. Rates of seizure response and seizure freedom at 12 months are reported according to concomitant use of sodium channel blockers (sodium channel blockers, *n* = 771; no sodium channel blockers, *n* = 130). Seizure response was defined as a ≥ 50% reduction in seizure frequency in comparison with baseline seizure frequency

Cannabidiol (CBD) and Clobazam (CLB)

- CBD can inhibit CYP 2C19, which metabolizes active metabolite of CLB, N-desmethyl-clobazam (N-CLB)
- N-CLB and CBD active metabolite (7-OH-CBD) are increased when CLB and CBD are co-administered. **Morrsion, Clin Pharmacol Drug Dev 2019**
- In one OL CBD trial, 51% of pts taking CLB had a ≥50% reduction in motor seizure frequency at 12 weeks, compared with 27% not taking CLB
- In a meta-analysis of phase 3 CBD clinical trials in Dravet syndrome and Lennox-Gastaut syndrome (429 CBD and 285 PCB patients), ≥ 50% reduction in seizure frequency during the treatment period was reported in 52.9% (vs 27.8% in placebo group) in those on CLB **vs** 29.1% (15.7% in the placebo group) among patients not on CLB. **Lattanzi, Epilepsia 2020**

Cenobamate (CNB) interactions

- CNB was marketed in 2020 for focal seizures- unusually high sz-free rate in clinical trials (CNB vs PCB: 27% vs 9.1%; 21% vs 1%)
- MOA: enhancing GABA, inhibiting persistent sodium current
- CNB inhibits CYP2C19; phenobarbital and phenytoin levels increase by a mean of 37% and 84%, following multiple CNB doses
- The clobazam metabolite N-desmethylclobazam (N-CLB) is also metabolized by CYP2C19 and may accumulate, resulting in sedation

CNB-CLB interaction- open label VUMC trial

Osborn & Abou-Khalil, Epilepsy & Behavior 2023

- CNB started in 6 pts on CLB 20-50 mg. Sedation began at CNB doses of 25-100 mg (100mg in 3, 50mg in 2, 25mg in 1)
- CLB was stopped in all. In the month before CLB was stopped, 5 were responders (3 >75% seizure reduction and 2 free of disabling seizures); 2 months after stopping CLB, only one patient still had >50% improvement
- CLB was restarted at 5 mg/d in 5 of the 6 patients. **At last FU 4 were continuing CLB; 2 were Sz-free and 2 were >50% responders**
- 5 other patients not responding on CNB added 5mg/d CLB: 2 had >50% reduction and 1 became Sz-free (>3 years); 2 stopped CLB due to adverse effects

CNB-CLB interaction- conclusion

Osborn & Abou-Khalil, Epilepsy & Behavior 2023

- Five patients who responded to the combination of clobazam and cenobamate had failed to respond to clobazam and cenobamate used independently
- **This suggests a synergistic pharmacodynamic interaction between clobazam and cenobamate**
- Pharmacokinetic interaction related to the ratio of N-desmethylclobazam to clobazam concentrations may play a role
  - Ratio, normally ≤12, was >100 in patients taking 200-400 mg of cenobamate

Analysis of the final medication adjustment leading to seizure freedom in patients treated with cenobamate

Abou-Khalil & Osborn, IEC 2025 abstract

- Identified final adjustment preceding seizure freedom in patients with previously drug-resistant focal epilepsy who had terminal remission for >3 months while taking cenobamate (CNB).
- 15/76 (19.7%) patients currently receiving CNB were seizure-free for >3 months (mean 29 months; range 4 to 73 m) at the last visit (mean baseline seizure frequency 7.6 seizures per month).
- The mean CNB dose at the time of seizure freedom was 262 mg (range 100 mg to 400 mg).

Final medication adjustment leading to seizure freedom in patients treated with CNB

Abou-Khalil & Osborn, IEC 2025 abstract

- Most commonly used concomitant ASMs: clobazam (13/15 patients) with a dose range of 2.5-15 mg (mean 8.3 mg).
- Other commonly used concomitant ASMs were lamotrigine (8 patients), levetiracetam (4 patients), lacosamide (3 patients).
- The most common last adjustment that led to seizure freedom was addition of cenobamate (4 patients), cenobamate dose increase (4 patients), increasing clobazam dose (4 patients), and addition of clobazam (2 patients).

Final medication adjustment leading to seizure freedom in patients treated with CNB

Abou-Khalil & Osborn, IEC 2025 abstract

- **5/6 patients who became seizure-free after addition or titration of clobazam had previously failed clobazam alone.**
- Findings support synergy between cenobamate and clobazam and support the strategy of addition/ titration of clobazam in patients who have not become seizure-free on cenobamate.
- In addition, the study supports continued cenobamate titration until seizure freedom or limit of tolerability.

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Epilepsia®

RESEARCH ARTICLE

Adjunctive cenobamate in people with focal onset seizures: Insights from the Italian Expanded Access Program

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Adjunctive cenobamate in people with focal onset seizures: Insights from the Italian Expanded Access Program

Roberti et al, Epilepsia 2024

- Retrospective study at 21 Italian centers; 236 subjects
- A higher percentage of responders was observed among subjects treated with clobazam (O.R. 2.02), although the difference was not statistically significant.
- The highest rates of cotreatment withdrawal and reductions in the daily dose were observed for Na channel blockers and GABA modulators (linked to pharmacokinetic interactions), and perampanel.
- The type of ASM associated did not influence CNB effectiveness except for a favorable trend with clobazam

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Quality of life and synergistic combinations of antiseizure medication in patients treated with cenobamate in early therapy lines for focal-onset seizures

Yaroslav Winter [a,b,1,*], Raya Abou Dargham [i,1], Erik Ellwardt [c], Thilo Hammen [d,j], Christoph Massing [e], Sarah Gößling [f], Marina Flotats-Bastardas [g], Sergiu Groppa [a], Michael Zemlin [g], Christopher Meudt [h]

CNB synergistic ASMs

Winter, Epilepsy & Behavior 2026

Comparison of drug load, seizure control and HrQoL by concomitant ASM in patients treated with cenobamate.

	Concomitant antiseizure medication in patients treated with cenobamate						
	LEV	BRV	CLB	VPA	LTG	LCS	ESL
N	22	18	15	14	12	9	6
(%)	(28.6)	(23.4)	(19.5)	(18.2)	(15.6)	(11.7)	(7.8)
Dose reduction, mg	56.8 ± 149.5	9.7 ± 14.8	11.3 ± 6.9	200.0 ± 309.4	70.8 ± 43.1	83.3 ± 57.7	266.7 ± 188.6
mean ± SD (median)	(0)	(0)	(15)	(0)	(50)	(100)	(400)
DDD reduction, %	2.9	7.6	53.3*	12.3	19.3	23.0	23.4
Seizure freedom, %	22.7	22.2	46.7*	14.3	8.3	12.2	16.7
Response rate, %	77.3	77.8	86.7*	57.1	58.3	66.7	66.7

- CNB demonstrated superior seizure control and HrQoL when combined with low-dose clobazam and a trend for combination with SV2A modulators.
- Low-dose clobazam can work synergistically with CNB. The combination with SV2A modulators showed a positive trend.

RESEARCH ARTICLE OPEN ACCESS

Cenobamate and Clobazam Combination as Personalized Medicine in Autoimmune-Associated Epilepsy With Anti-Gad65 Antibodies

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CNB and CLB Combination in Autoimmune-Associated Epilepsy With Anti-GAD 65 Antibodies

Serrano-Castro, Neurol Neuroimmunol Neuroinflamm 2023

- 8 patients with anti-GAD Abs and highly refractory epilepsy, who failed a mean of 9.5 (SD = 3.2) ASM without sustained seizure control.
- Ave monthly seizure frequency in 3 months before CNB: 19.63.
- After introduction of CNB all pts improved- 92% median seizure reduction (mean FU 156.75 days).
  - **Median % seizure reduction with CNB higher with (6 pts) than without (2 pts) concomitant CLB: 94.72% vs 41.50% (p = 0.044) and also higher than control group (20 pts) with refractory epilepsy not related to anti-GAD65 treated with the same combination: 45% (p = 0.019).**
- ?Precision medicine to correct the imbalance due to the GABAergic stimulation deficit in postsynaptic neurons

Seizure: European Journal of Epilepsy 136 (2026) 102–106

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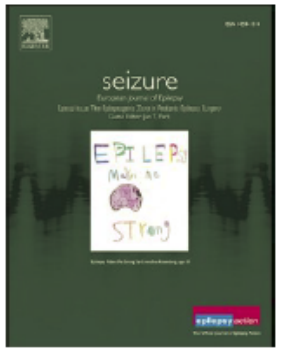

Efficacy and safety of cenobamate-based combination therapy in drug-resistant epilepsy: Secondary analysis by mechanisms of action of concomitant antiseizure medications

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CNB based combinations

Bosak, Seizure 2026

- 475 adults with drug-resistant epilepsy treated with adjunctive CNB
- Adjunctive ASMs classified as Na channel blockers (SCBs), SV2A ligands, VPA, carbonic anhydrase inhibitors, or GABA analogs.
- Baseline use of VPA associated with higher odds of ≥50 % seizure reduction and seizure freedom, whereas SCB was associated with lower odds of seizure freedom.
- Presence of SV2A ligands, VPA, or carbonic anhydrase inhibitors was correlated with lower treatment discontinuation rate
- CNB dose showed no significant association with achieving ≥50 % response, seizure freedom, or overall AE occurrence

Three-drug combination therapies

Wu, Neurotherapeutics 2024

- Single-center, longitudinal observational study of 511 triple trials (76 regimens) among 323 patients with drug-resistant focal epilepsy
- Effectiveness of combinations analyzed using seizure-free rate and within-patient ratio of seizure frequency (SFR <1 indicated superior efficacy).
- At the last visit, 48 pts (14.9%) achieved seizure freedom.
- **LTG/VPA/TPM (n=95, 29.4%) and LTG/VPA/LEV exhibited the highest seizure-free rates at 17.9% and 12.8% (SFR 0.48 and 0.63).**
- LTG/VPA/PER was another promising regimen (median SFR = 0.67)
- **Incidence of regimen-specific side effects lowest with LTG/VPA/LEV (5.1%, 2/39)**, intermediate with LTG/VPA/TPM (17%); highest with LTG/VPA/PhB (40.0%, 4/10).

Rational polytherapy conclusions

- Unfavorable ASM combinations exist
- "Rational" ASM combinations should
  - Avoid adverse pharmacokinetic interactions
  - Include different mechanisms
  - Avoid combining two sodium channel blockers, mainly because of toxicity
- There is strong clinical evidence for synergism in LTG-VPA combination; more limited clinical evidence favors a few other ASM combinations: VPA-ESX, LEV-LTG, CBD-CLB, CNB-CLB
- Better understanding of epilepsy pathophysiology and ASM mechanisms will help refine the science of ASM rational polytherapy