Difficult to treat childhood epilepsy: Lessons from clinical case scenario

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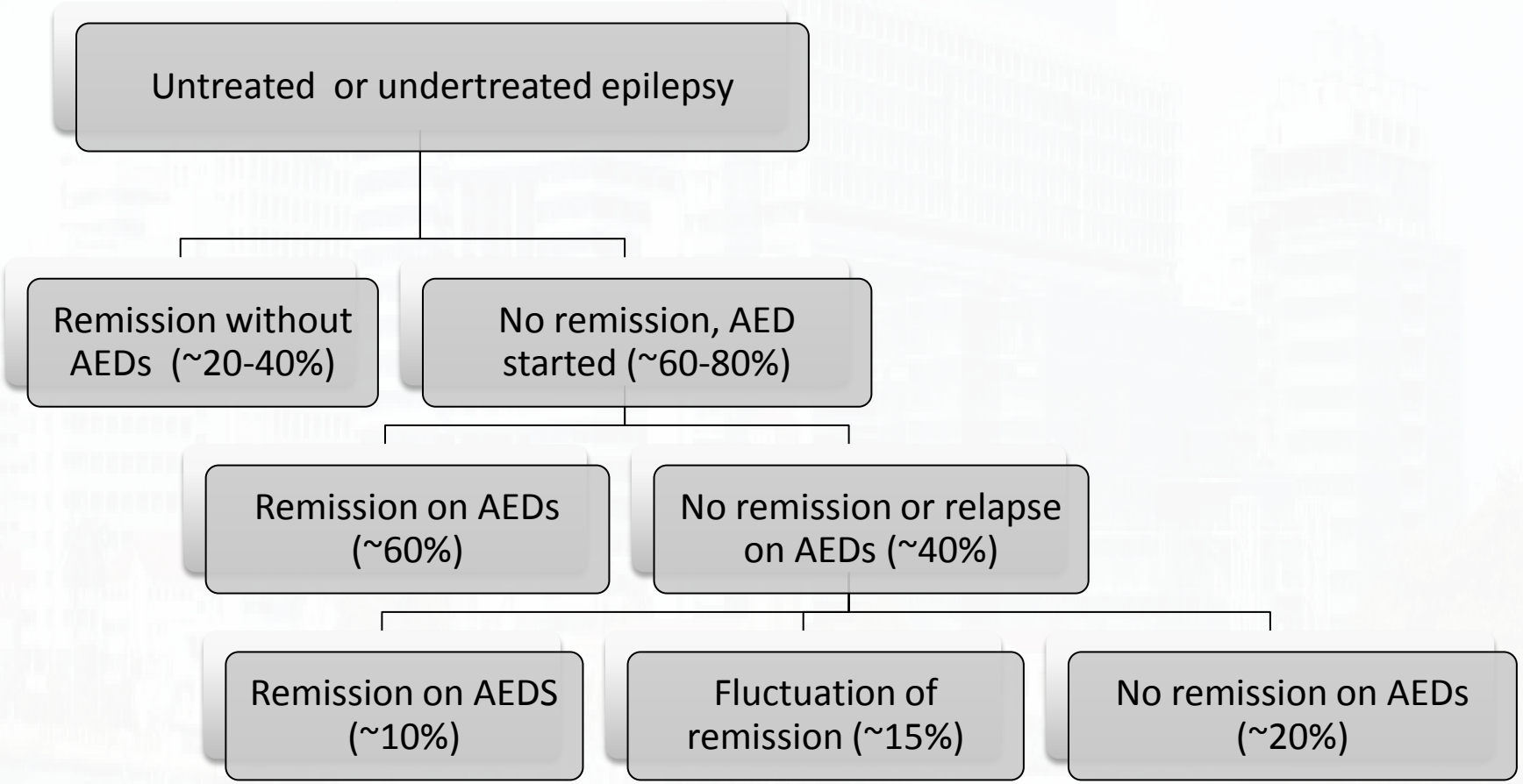
Natural history of Epilepsy



Schmidt D, Sillanpaa M. Evidence-based review on the natural history of the epilepsies. Curr Opin Neurol 2012, 25: 159-163

Consequence of refractory epilepsy

- Injury
- Disability
- Increase mortality
- Psychosocial disabilities
  - Under-education
  - Underemployment & unemployment
  - Impaired socialization
  - Psychiatric disturbance

Sperling MR. CNS Spectr 2004;9:98 –109.
Jacoby A, et al. Epilepsia 1996;37:148 –161.

Drug-resistant epilepsy

- "Failure of **adequate** trials of 2 **tolerated**, **appropriately** chosen and used antiepileptic drug schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom"
  - Appropriate
    - Right medication
    - Right dose
    - Reasonable time
  - Tolerated
    - Minimal or tolerable side effects

Kwan P, et al. Definition of drug resistant epilepsy: Epilepsia 2010;51:1069–1077.

Before making diagnosis: make sure that

- Seizure is diagnosed correctly
  - Epileptic seizure : Focal or generalized
    : Epileptic syndrome
  - Non-epileptic seizure
  - Or have both
- Choose right AED
  - Right medication
  - Right dose
- Good compliance
- AED in therapeutic level

Check lists

- Correct diagnosis? : Carefully characterize seizure
  - Epileptic/non-epileptic?
  - Epileptic: Focal or generalized?
  - Epileptic syndrome?
- Appropriate medication?
  - Right medication?
  - Compliance?
  - Right dose?
  - Appropriate level?
- Any precipitating factors: sleep deprivation, fatigue, etc. ?
- Is it really intractable?
- Anything we can offer: surgery/KD/VNS

Pitfall

- Beware of non-epileptic events
- Incorrect seizure type diagnosis
  - Inappropriate medication
- Inappropriate epileptic syndrome
  - Inappropriate medication
- Poor compliance
- Different bioavailability among patients

AEDs that can aggravate certain seizures

- Absence
  - PHT, CBZ,
  - OXC, VGB, TGB, GBP
- Myoclonic
  - PHT, CBZ
  - OXC, LTG, GBP, VGB
- Atonic/Tonic seizure
  - PHT, CBZ, OXC

Sazgar M, Bourgeois BFD. Aggravation of Epilepsy By Antiepileptic Drugs. Pediatr Neurol 2005;33:227-234.

AEDs that aggravate seizure in certain epileptic syndrome

- ECSW/LKS
  - CBZ, PHT
- PME
  - PHT, CBZ
- LGS/MAE
  - CBZ, PHT, VGB, BDZ
  - OXC, LTG, GBP
- SMEI
  - LTG, CBZ, VGB
- JME
  - CBZ, PHT
  - OXC, LTG

Sazgar M, Bourgeois BFD. Aggravation of Epilepsy By Antiepileptic Drugs. Pediatr Neurol 2005;33:227-234.

Devastating epileptic syndrome

- EIEE/EME
- SMEI
- Migratory partial seizure of infancy
- West syndrome
- LGS
- In these patients, it is more practical to set up an appropriate and realistic goal of treatment rather than to complete seizure control

How to use combination

- Establish optimal dose of baseline agent
- Add drug with multiple mechanisms
- Avoid combining similar modes of action
- Titrate new agent slowly and carefully
- Be prepared to reduce dose of original drug
- Replace less effective drug if response still poor
- Try range of different duotherapies
- Add third drug if still sub-optimal control
- Devise palliative strategy for refractory epilepsy

Brodie MJ, Sills GJ. Combining antiepileptic drugs—Rational polytherapy? Seizure: 2011; 369-375

AED: Mechanism of actions

Sodium channel blockers

- Fast-inactivated state—PHT, CBZ, LTG, OXC, ELCBZ
- Slow-inactivated state—LCS

Calcium channel blockers

- Low voltage activated channel—ETS
- High voltage activated channel—GBP, PGB

GABA-ergic drugs

- Prolongs chloride channel opening—PB
- Increased frequency of chloride channel opening—BZP
- Inhibits GABA-transaminase—VGB
- Blocks synaptic GABA reuptake—TGB

AED: Mechanism of actions

Synaptic vesicle protein 2A modulation

LEV

Carbonic anhydrase inhibition

ACTZ

Multiple pharmacological targets

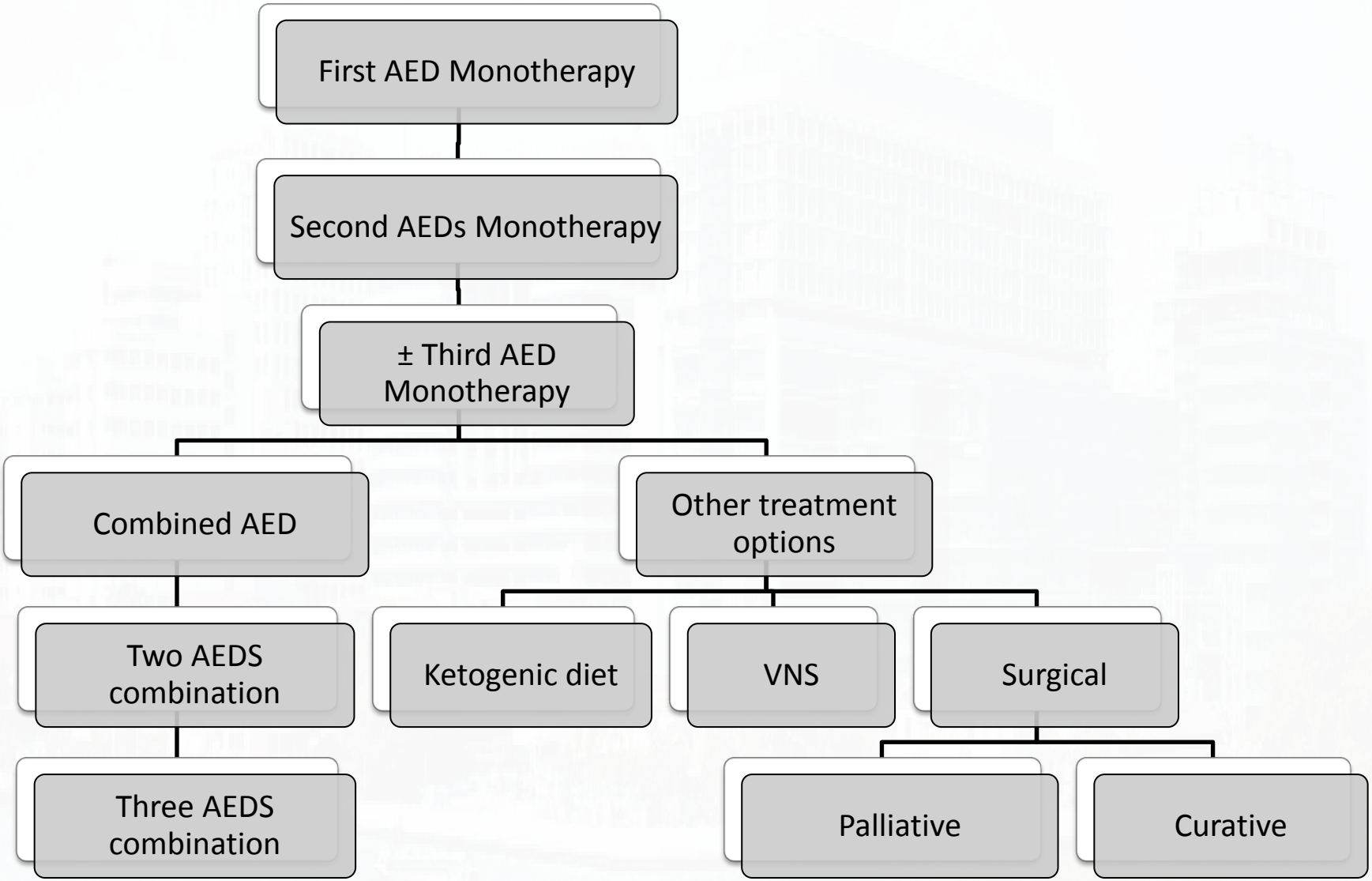
VPA, FBM, TPM, ZNS, RFN

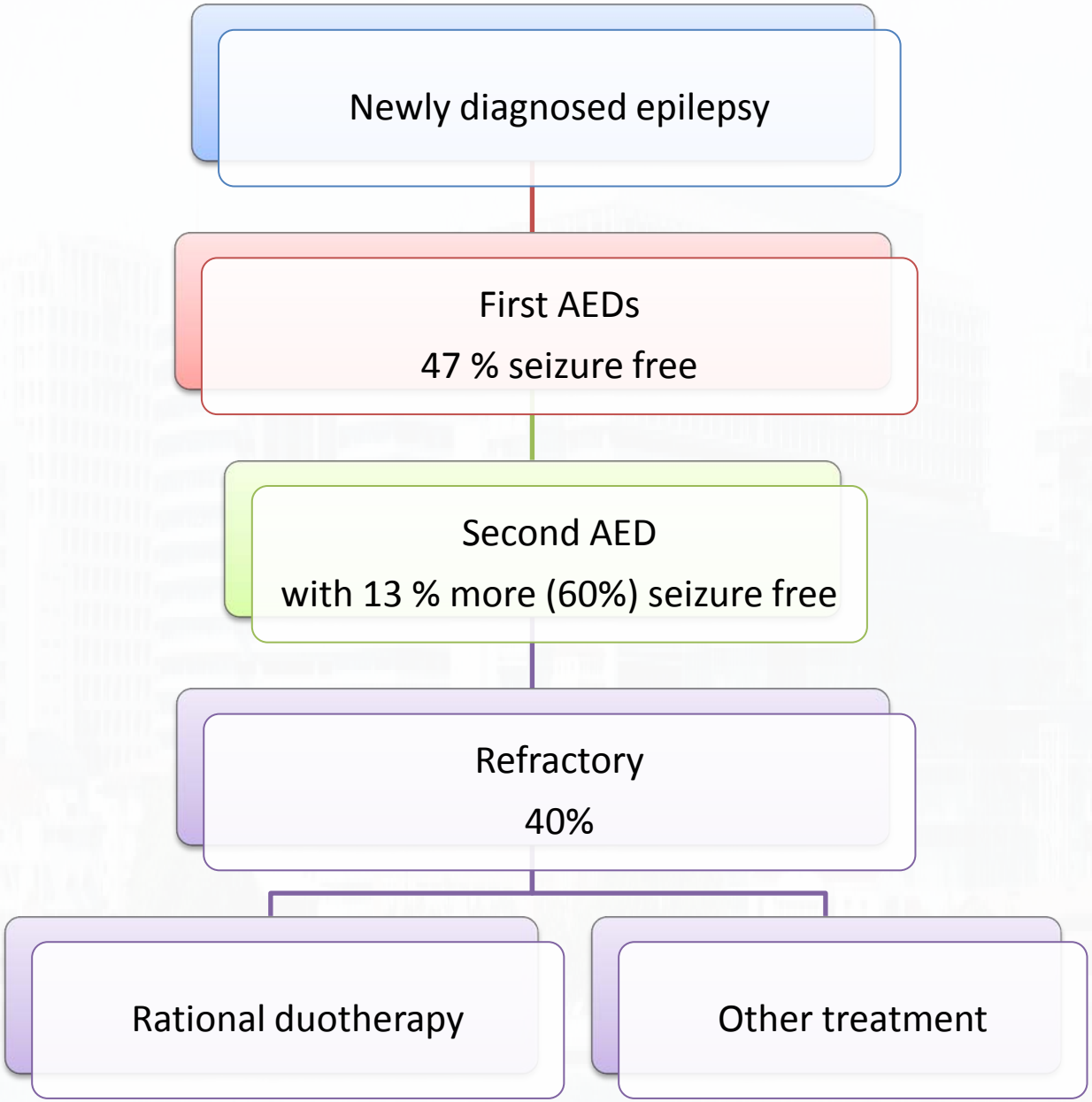
Potassium channel activity

RTG

AMPA

PRP


First AED Monotherapy
Second AEDs Monotherapy
± Third AED Monotherapy
Combined AED
Other treatment options
Two AEDS combination
Three AEDS combination
Ketogenic diet
VNS
Surgical
Palliative
Curative



Kwan P, Brodie MJ. N Engl J Med 2000;342:314-9

What combination should we use?

- With current available AEDs
  - ~ 200 combination with 2 AEDs
  - ~ 1000 combinations with 3 AEDs

Combining antiepileptic drugs—Rational polytherapy?
Brodie MJ, Sills GJ. Seizure; 2011:369-75

- Is there any good combination with
  - Additive or supra-additive effects
- Data can be analyzed from
  - Animal data
  - Clinical data

Probably advantage

Efficacy	Side effects	Other (cost, regimen, SE, teratogenicity)
Additive	Less than additive	No or minimal disadvantage
Supra-additive	Less than additive	No, minimal, or moderate disadvantage
Supra-additive	Additive	No or minimal disadvantage

Rational polytherapy. Jacqueline A. French JA, Faught E. Epilepsia, 50(Suppl. 8):63–68, 2009

Probably disadvantage with polytherapy

Efficacy	Side effects	Other (cost, regimen, SE, teratogenicity
No advantage or worsening	Additive	No, minimal, or moderate disadvantage
Less than additive	Additive	No, minimal, or moderate disadvantage
Additive	Supra-additive	No, minimal, or moderate disadvantage
Less than additive or additive	Additive	Major disadvantage

Rational polytherapy. Jacqueline A. French JA, Faught E. Epilepsia, 50(Suppl. 8):63–68, 2009

Animal data: synergistic

Valproate

- + phenytoin
- + ethosuximide,
- + lamotrigine
- + topiramate
- + Gabapentin

Carbamazepine

- + gabapentin,
- +topiramate

Oxcarbazepine

- +topiramate
- + oxcarbazepine
- + gabapentin
- + Levetiracetam

- Levetiracetam + topiramate
- Tiagabine + gabapentin
- Lamotrigine + topiramate

Pharmacodynamic interactions between antiepileptic drugs: preclinical data based on Isobolography .
Czuczwar SJ, et al. Expert Opin. Drug Metab. Toxicol. (2009) 5 (2):131-136

Animal data:

Antagonist

- Carbamazepine + Lamotrigine
- Carbamazepine + Oxcarbazepine

Variable result

- Oxcarbazepine + Clonazepam

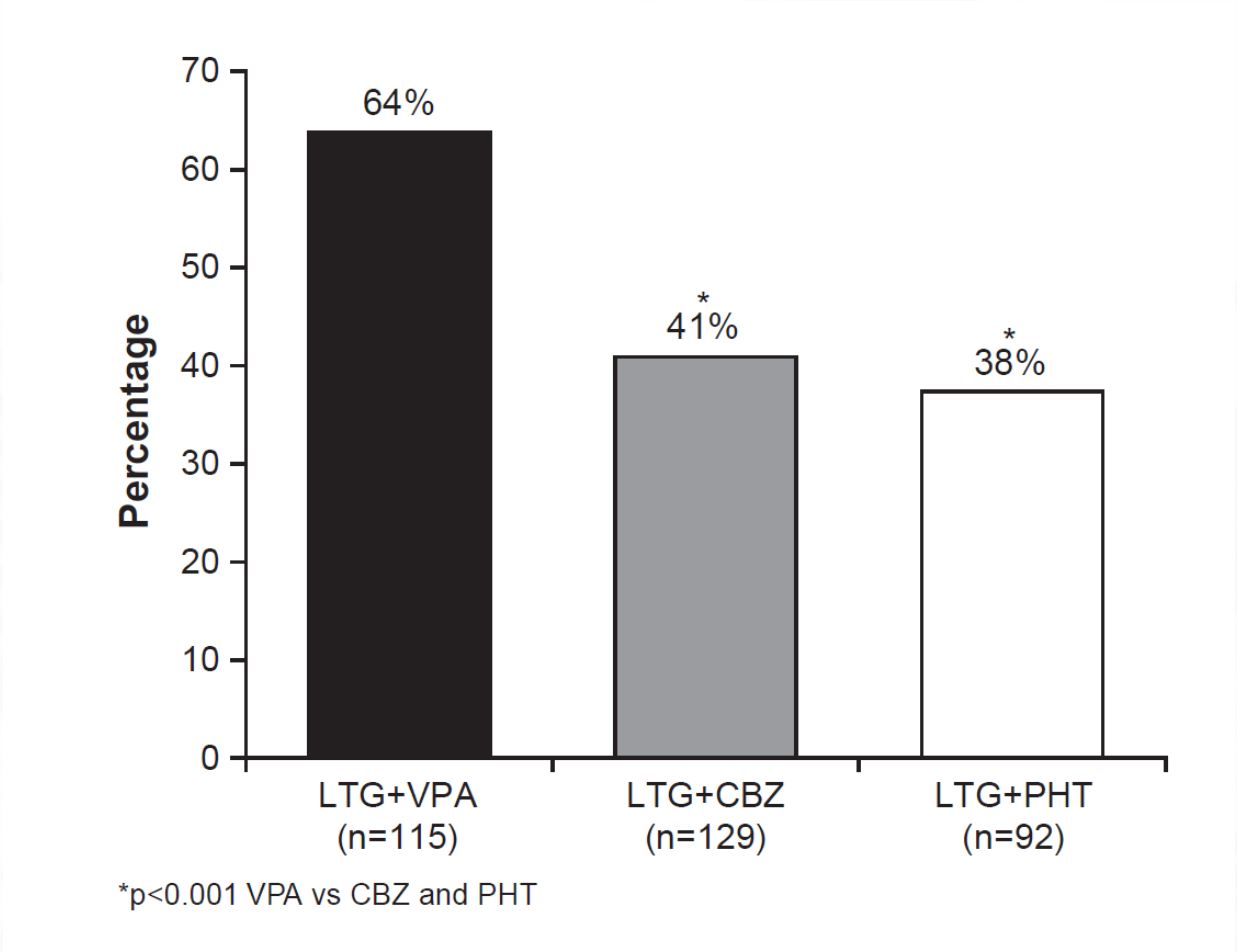
Pharmacodynamic interactions between antiepileptic drugs: preclinical data based on Isobolography . Czuczwar SJ, et al. Expert Opin. Drug Metab. Toxicol. (2009) 5 (2):131-136

Duotherapy with seizure free

AED	Focal	Generalized	Total (%)
LTG + VPA	59	37	96 (24.3)
CBZ + VPA	12	14	26 (6.6)
PB + PHT	11	13	24 (6.1)
CBZ + LEV	19	4	23 (5.8)
CBZ + TPM	16	4	20 (5.1)
LEV + LTG	15	4	19 (4.8)
LEV + VPA	9	7	16 (4.1)
LTG + TPM	9	5	14 (3.5)
CBZ + PB	7	6	13 (3.3)
CBZ + GBP	10	2	(3.0)
Others	81	51	132 (33.4)

Antiepileptic drug combinations——Have newer agents altered clinical outcomes?
Stephen LJ, Forsyth M, Kelly K,Brodie MJ. Epilepsy Research (2012) 98, 194—198

Clinical Data



Lamotrigine substitution study: evidence for synergism with sodium valproate?
M.J. Brodie MJ, Yuen A.W.C., 105 Study Group. Epilepsy Research 26 (1997) 423–432