Rational polytherapy and drug interactions of antiepileptic drugs

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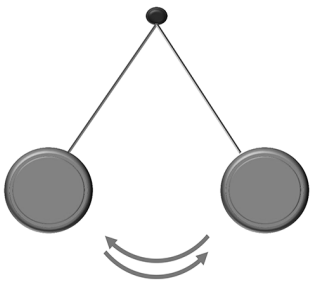
I. MODE of AEDs Therapy



Monotherapy VS. Polytherapy

- A full dose of one drug achieves better Sz control with fewer AEs
- Combination of AEDs of lower doses provide higher efficacy with less toxicities.

I. MODE of AEDs Therapy
(1) Evolution of Monotherapy

- **Before 1980, Polytherapy >>> Monotherapy**
  - A survey by Guelaen et al. *(Clinical Pharmacology of AEDs; eds., H Schneider et al., Springer-Verlag, 1975:2-10)* in early 1970's revealed that a patient took 3 AEDs in average(n=11,720 from 15 centers in Europe).
- **Introduction of "TDM" and "CBZ and VPA" in 1970's triggered the emergence of optimal monotherapy**
  - **Reynolds et al.** *(Lancet 1976;1:923-926)*
    - Among 31 Pts under PHT monotherapy, Szs were uncontrolled in 11 pts but 8 of them had subtherapeutic blood level.
  - **Shorvon and Reynolds** *(BMJ 1979;2:1023-1025)*
    - Trial of conversion to monotherapy in 40 pts under polytherapy
      - Successful conversion in 29 pts (72%) with Sz improvement in 16 pts (55%) and improvement of AEs in 16 pts (55%)

(1) Evolution of Monotherapy

- **Schmidt D** *(J N NS Psy 1982 and 1983)*

SZ outcome	Add-on of 2nd drug (30 pts under max. monotherapy)	Conversion to monotherapy (36 pts under max. 2 drug therapy)
Sz improved	11 pts (37%)	13 pts (36%)
No change	12 pts (40%)	17 pts (47%)
Worse	7 pts (23%)	6 pts (17%)
AE	?	Total No of AEs: decreased No of pts with AEs: unchanged

- **Schmidt and Richter** *(Ann Neurol 1986;16:85-87)*
  Alterative monotherapy in 59 pts with refractory epilepsy:
  - ≥ 75% of Sz freq reduction in 19 pts (31%)
  - improvement of AEs in 16 pts (27%)

(1) Evolution of Monotherapy
-Summary-

- **Monotherapy of Optimal Dose** provides advantages of
  - *Less chance of immediate and delayed AEs.*
  - *Avoid drug interactions precipitating drug toxicities and/or Sz worsening.*
  - *Simpler regimen for accurate assessment of responses to individual drugs, better compliance and less costly.*
- In patients who failed to a monotherapy, '**Alternative Monotherapy**' is effective and preferred to combination therapy

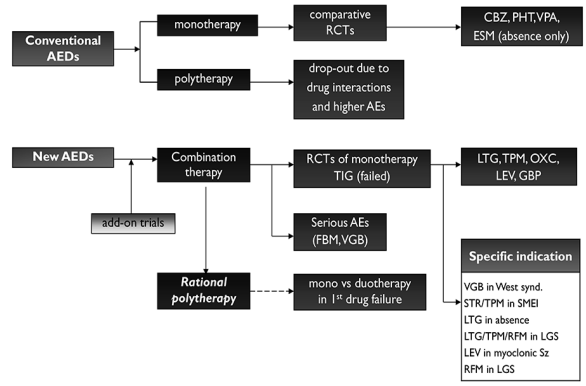
- Most patients do not require polytherapy -

I. MODE of AEDs Therapy
(2) Revival of Polytherapy

- **Introduction of New AEDs**

1857	Bromides	1989	Vigabatrin, Zonisamide
1912	Phenobarbital	1993	Felbamate, Gabapentin
1938	Phenytoin	1995	Lamotrigine
1952	Acetazolamide	1996	Topiramate
1954	Primidone	1997	Tiagabine
1960	Ethosuximide	1998	Oxcarbazepine
1961	Diazepam & other BZDs	2000	Levetiracetam
1970s	Carbamazepine Valproate	2005	Pregabalin
		2007	Stiripentol, Rufinamide (as orphan drug)
		2008	Lacosamide
		2009	Eslicarbazepine
		2011	Retigabine
		2012	Perampanel
		On waiting	Brivaracetam

Clinical Development of AEDs: *Old vs. New*



♣ Case Scenario *(Stephen et al, Lancet 1998)*

- 18 y.o M with 1 to 2 Szs (CPS ± 2GTCS)/week under PHT-monotherapy
  - trial of several AEDs & Lt ATL
  - referred to the Epilepsy Clinic in 1992
    - add-on Vigabatrin – no help to D/C
    - add-on LTG: minimal Sz reduction
      → change to LTH monotherapy 800mg/day (D/C PHT)
    - add-on TPM: 75mg/day → Sz Free Since

- Why "Sz Free" after TPM add-on?
  - *due to effects of TPM alone?*
  - *due to phamacodynamic interaction of LTG and TPM?*
  - *due to a part of natural course?*

Case Scenario

- 41 y.o. male with a 14 year history of supplementary motor area(SMA) seizures consisting of bilateral internal rotation of feet, fencing posture with the right arm extended and left arm flexed, head to the right.
  - frequency : 5-10/ nights
  - Current AED: LTG 400mg/day
  - Previously failed to PB, PHT, and CBZ in monotherapy and combination therapy
  - MRI: normal
  - EEG: interictal: SWs at Fz and Cz
    ictal: bilateral beta activity at onset
  - Seiure free after add-on of VPA to LTG

- ***Questions?***
  - Why did he respond to the combination of VPA+LTG but not others?
  - Is this combination more effective in FLE or SMA seizures?
  - Why is this combination effective?
    - due to Pharmacokinetic or Pharmacodynamic interaction?
    - any known mechanisms?

(2) Revival of Polytherapy
- EBM of New AEDs -

- New AEDs were found effective in add-on trials of highly refractory epilepsy patients taking one to three AEDs
  - Sz free rate: ~5% (LEV, TPM > other AEDs)
  - > 50% Sz freq reduction: ~20%(after minus placebo)

- Effectiveness of New AEDs *vs.* Conventional AEDs were largely equivalent in initial monotherapy
  - efficacy: New AEDs ≤ Old AEDs
  - tolerability: New AEDs ≥ Old AEDs

- Pharmacological Properties: New AEDs > Conventional AEDs
  - Multiple and diverse ***Mechanisms of Actions***
  - Less potentials of ***Pharmacokinetic Interactions***

2. Revival of Polytherapy

♣ **Concept of Total Drug Load** *(Lammers at al. Epilepsia 1995:36:440-446)*

- Total Drug Load (TDL): Ratio of *'prescribed daily dose(PDD)'* to *'defined daily dose(DDD)'* by WHO-guideline
- Measurement of AEs by Neurotoxicity index and Systemic toxicity index
  → correlates with stratified TDL in clinic patients
  - TDL≤2/day: 169 pts in Monotherapy, 120 pts in Polytherapy
    no differences in AE-index
  - TDL>2/day: 134 pts in Polytherapy: AEs in 70%~100%
  - TDL≥4/day: All pts represented Aes

<Conclusion>

Higher incidence of AE in patients under polytherapy is related to higher TDL

- *if TDL is kept < 2.0/day, AEs are comparable*
- *patients under monotherapy cannot tolerate TDL>2.0/day, while patients under polytherapy may better tolerate higher TDL*

II. "Monotherapy" vs. "Polytherapy"
- Controversies -

- Which modality is better and When?
  - initial treatment
  - after the first drug failure
  - after the 2nd drugs failure (or in DREs)
- Which drugs for Combination?
  → concept of ***"Rational Polytherapy"***

II. "Monotherapy" vs "Polytherapy", *which is Better?*
(1) Patients with Newly Diagnosed Epilepsy

♣ **Deckers et al.** *(Epilepsia 2001;42:1187-1394)*

- DBRCT of CBZ 400mg vs CBZ 200mg + VPA 300mg(n=125)
- No differences in efficacy, tolerability and QOL

▪ **Completion Ratio**
61% in Mono vs 70% in Poly (p=0.16)

▪ **Withdrawal due to AEs**
14% in Mono vs 22% in Poly (p=0.15)

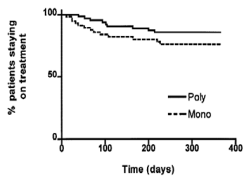


FIG. 2. Survival curve for patients staying on treatment.

❖ **Conclusion:**
No differences between "CBZ" and "CBZ+VPA" at equivalent TDL(PDD/DDD)
(a small trend for better to of tolerability "CBZ+VPA")

II. Monotherapy vs Polytherapy, *Which is Better?*
(2) After First Drug Failure

- **Two drug combination vs 2nd drug monotherapy?**
  - **No controlled trials, but review by Deckers et al. (2003)**
    - SFR: 25% (12-45%) in 4 substitution Therapy (n=159)
      23% (15-35%) in 5 duotherapy (n=131)
  - **Expert's Opinion on the Treatment Strategy**

Authors	2nd Drug Treatment	3rd Drug Treatment
Semah et al. (France, 2004)	Monotherapy (52%)	-
Karceski et al. (USA, 2005)	Monotherapy (98%)	Monotherapy (72%)
Song et al. (Korea, 2007)	Monotherapy (75%)	Combination (92%)
Legros et al. (Belgium, 2009)	Monotherapy (66%)	Combination (83%)

II. Monotherapy vs Polytherapy, *Which is Better?*
(2) Patients Failed to First Drug

♣ **A single center observation study** *(Kwan and Brodie, Seizure 2000;9:464-468)*

- n = 77 who failed to well tolerated first drug

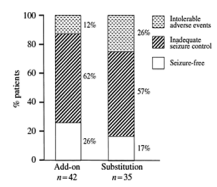


Fig. 3: Response to add-on or substitution in patients with inadequate seizure control on the first well tolerated antiepileptic drug.

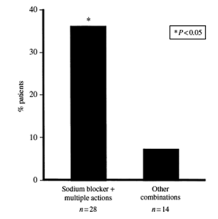


Fig. 4: Response to different combinations of antiepileptic drugs according to mechanisms of action.

- **Conclusion:** *Combination Therapy consisting of Na-channel blocker and multiple action mechanisms seems to provide better outcome than Substituion Monotherapy after the First Drug Failure*

(2) Patient Failed to First Drug

- *Beghi et al.* *(Epilepsy Res 2003;57:1-13)*
  - An open, randomized trial(76pts in Mono vs 81pts in Poly)

RESULTS	Monotherapy	Polytherapy	P-value
Retention at 12mo	55%	65%	0.74
12mo SF	14%	16%	0.74
AE: incidence	51%	37%	0.07
Withdrawal	10.5%	6.2%	

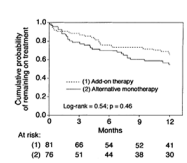


Fig. 1. Cumulative time-dependent probability of remaining on the allocated treatment in the two study groups.

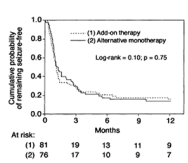


Fig. 2. Cumulative time-dependent probability of remaining seizure-free after achieving the target dose in the two study groups.

- **Conclusion:** *Comparable efficacy between Combination and Substitution monotherapy with a trend of better tolerability of Combination Treatment*

(2) Patient Failed to First Drug

♣ **Italian Multicenter Prospective Observational Study**
(Millul at el, Epilepsy & Behavior 2013;28:494-500)

- **n = 331from 58 centers in Italy, who failed to the 1st monotherapy**
  (nonrandomized pragmatic trial)

Outcome	Monotherapy(n=239)	Combination therapy(n=92)
Mean retention time	454.4±11.1	447.4±16.4
Treatment failure	65 (27.2%)	23 (25.0%)
12mo SFR	128 (53.6%)	47 (51.1%)
Report of AEs	111 (46.4%)	37 (40.2%)
Withdrawal due to AE	19 (29.2%)	6 (26.1%)

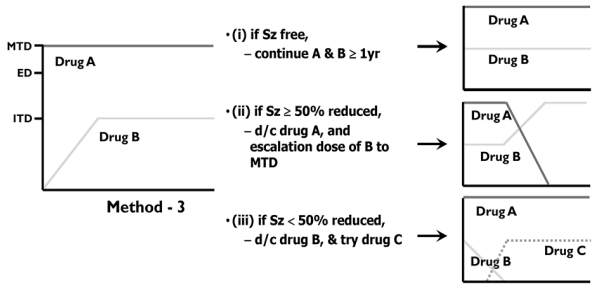
- Physician' explanation for Substitution Monotherapy;
  better tolerability(59.8%), greater efficacy(26.4%), better tolerability and greater efficacy(7.1%)
- Physician's explanation for add-on therapy: *greater efficacy (100%)*

- **Conclusion:** *Comparable Effectiveness between Mono and Combination Therapy. AEs were not higher in polytherapy*

II. 'Monotherapy' vs. 'Polytherapy', *Which is Better?*
(2) Patients Failed to First Drug

- No RCTs yet
- No evidence of differences in efficacy and tolerability
  - Suggestion of better tolerability in Polytherapy and better efficacy in specific drug combination(Na channel block + multiple MOA)
- Sensible Approach
  - If first drug failed due to "LOE": Poly = Mono
  - If first drug failed due to "AEs": Mono ›› Poly
- The process of 2nd drug trial regimens a period of "Transient Polytherapy", Whose response may help making a future AEDs therapy

AEDs Therapy Based on 'Response to Transient Polytherapy'



❖ **Cons:** *risk of drug overdose and interactions at the beginning*
- require slow dose adjustment and close monitoring
Longer time for assessment of drug B

❖ **Pros:** *lower risk of Sz worsening*
assessment of synergistic action of combination therapy
more acceptable to patients

II. "Monotherapy" vs. "Polytherapy", *Which is Better?*
(3) Patients Failed to Second Drug

Authors	2nd Drug Treatment	3rd Drug Treatment
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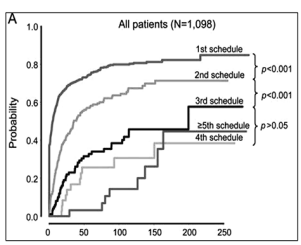
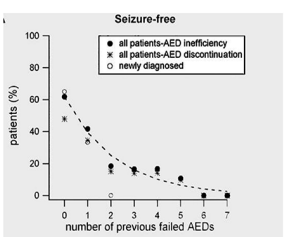
II. 'Monotherapy' vs. 'Polytherapy', *Which is Better?*
(3) Patients Failed to Second Drug

- **ILAE Consensus Proposal on Medical Intractability**
  - **Failure of adequate trials of 2 AEDs**
    - Well tolerated
    - Appropriately chosen and used schedules
  - **Failure to achieve sustained Sz freedom**
    - ≥ 3 times of the longest interseizure interval or ≥ 1 yr (choose the longer one)

Response to Successive Drug Regimens

- Brodie et al. (Neurology 2012)
  - Significant difference in the probability of SF between 1st and 2nd drug and 2nd and 3rd drug
  - Not significant between 3rd and 4th or 5th drugs
- Schiller and Najjar (Neurology, 2008)
  - SFR to AEDs therapy
    - 61.8% to first drug
    - 41.7% after failure of 1st drug
    - ~16% per regimen after failure of 2nd drug





(3) Patients Failed to the Second AEDs
- *Seizure Outcomes* -

♣ **Berg et al.** *(Ann Neurol 65:510-519)*
- n=128; f/u for 10.1yrs (med) after failure to first 2 AEDs.
- 73 (57%) experienced remission ≥ 1yrs
  - → relapse in 50 of 73 pts (68%) but often regained remission
  - → terminal 1yr remission in 48 (38%)
  - → ***terminal 3yr remission in 28 (22%)***
  - → Prognostic factor : for ≥ 1yr remission : idiopathic epilepsy (RR 3.64, p<0.0001)
    low Sz frequency (RR 2.57, P=0.008)
    3yr terminal remission : *symptomatic epilepsy (33% vs 11%: RR=0.76, p=0.003)*
- ***Conclusion:*** Sz remission ≥ 1yr often occurs after failure to first two-drug trials, but about 2/3 of them may relapse
  Repeating "Remission and relapse" is common
  Symptomatic epilepsy carries poorer outcome after failure of 2 AEDs

♣ **Wirrell et al.** *(Epilepsia 2013:54:1056-1064)*
- 79 of 381 children (19.7%) : "early medical intractability" defined as (i) Sz freq>1/6 mo, (ii) failure to ≥ 2 AEDs within 2 yrs of diagnosis
- Long-term outcome (median f/u = 11.7 yrs)
  34(45.3%) remained medically intractable
  34(45.3%) SF with or without AEDs
  7(9.3%) rare Szs only

Table 5. Probability of achieving seizure freedom without surgical intervention in patients with *early medical intractability*

Neuroimaging	Probability	95% lower	95% upper
Abnormal	0.09	0.03	0.23
Normal	0.60	0.44	0.74

➢ ***Neuroimaging abnormality:*** the single important predictor of enduring medical intractability (RR:7.0:2.30-21.24, p=0.0006)

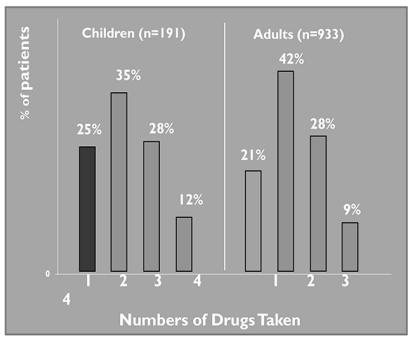
Outcome of AEDs therapy in DREs

- Patients who were not operable after surgical assessment
  - N=34, SF≥2.5yrs at 4yr-F/U in 21% *(Selwa et al, Epilepsia 2003;44:1568-72)*
  - N=49, SF≥1.0yr at 5yr-F/U in 24% *(Bien et al, Epilepsia 2006;47:1865-9)*
- Patients with DREs at Epilepsy Centers
  - Luciano and Shorvon *(Ann Neural 2007;62:375-381)*
    - 265 trials of add-on of new AEDs in 155 patients
    - ≥1 Sz/mo, Sz duration≥5yrs, mean F/U:18.3mo
    - SF in 28% of all pts(n=155) or 16% of each drug introduction (n=265)
  - Callaghan et al. *(Epilepsia 2011;52:619-626)*
    - 246 pts, ≥1 Sz/mo, failure to≥2AEDs, med F/U:5.9yrs
    - SFR in 33.4% at 7yrs of F/U (~5%/YR)
    - Relapse after remission in 34 of 59 patients (68%)
    - 61.7% of those relapsed had lower Sz frequency (<1Sz/mo)
  - Choi et al. *(Epilepsy Res 2011;93:115-119)*
    - n=187 pts, ≥1Sz/mo, failure to ≥2AEDs, med F/U:7yrs
    - SFR in 13% (25pts) at mean F/U of 5.9yrs (~4%/yr)
    - Relapse after remission in 15 pts (60%)
    - ~50% of those relapsed had lower Sz frequency than baseline
  - Cho et al. *(Epilepsia 2009;50:1910-19)*
    - n=125 pts, ≥1Sz/mo, failure to ≥2AEDs, Sz duration > 3yrs
    - SFR (≥ 1yr): 30.4% for 5yr-f/u
    - Terminal 1yr-SF at 5yr-f/u: 12.8% ITTA (20.8% in PPA)

II. 'Monotherapy' vs. 'Polytherapy', *Which is Better?*
(3) Patients Failed to Second Drug

Polytherapy is the major mode of therapy

- **Use of AEDs in 1,124 consecutive DREs**

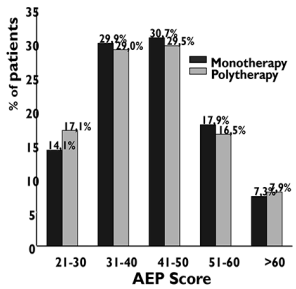


SOPHIE Study Group; Epilepsia 2010;51;921

Is polytherapy causing more AEs?

- AEs were not related to any specific AEDs, the number of AEDs, total drug loads, age, Sz frequency, etc.
- AEs were related to female gender and depressed mood.

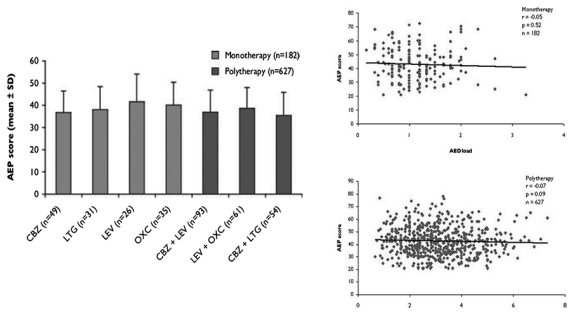
Burden of AEs in adult pts with DRE (N=790)



SOPHIE Study Group; Epilepsia 2010;51;797

Adverse Events in Monotherapy vs. Polytherapy
(SOPHIE Study Group : Epilepsia 2010;51;797-804)

- **In a naturalistic setting in which physicians are able to achieve the best compromise between Sz control and AEs, no major differences may be expected in toxicity burden among patients receiving different regimens.**



II. 'Monotherapy' vs. 'Polytherapy', *Which is Better?*
- Summary -

- No RCTs & no class I/II evidence for any differences
- Monotherapy is preferred in newly diagnosed patients and in patients who is poorly tolerate the first drug
- In patients who failed to the first drug which was well tolerable, transient combination therapy is a more practical option
- In patients who failed to 2nd drug(DRE), polytherapy is the major mode of therapy

❖ Since the era of "New AEDs", polytherapy is gaining more acceptance for their diverse MOA, less pharmacokinetic interactions, and better tolerability → **"Rational Polytherapy"**

III. Rational Approach for AED Combination

- ***Polytherapy is the Major Mode of Therapy in DREs***
  - **Objectives:**
    - To achieve (or improve) Sz control in patients refractory to previous AEDs therapy
    - To provide better tolerability when monotherapy is poorly tolerable
  - **How to choose "Drugs for Combination?"**
    - With 20 currently recognized AEDs, ***190 combinations*** are possible for duotherapy and ***1,140 possible combinations*** for triple therapy !
    - Not all drug combinations are equal !

- Features of Ideal AED Combination -

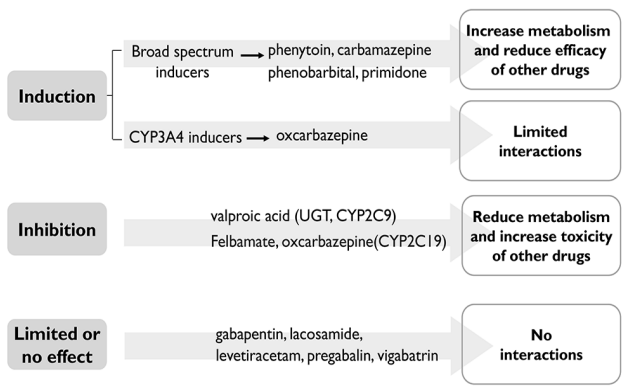
- No pharmacokinetic interactions
- Positive(or Synergistic) Pharmacodynamic Interaction
  - Supra - additive efficacy
  - Infra - additive toxicity
- Avoid drugs having same AEs profile

Improve Therapeutic Index

I. Pharmacokinetic Interactions

- Common, usually due to 'enzyme induction or inhibition'
  - ☞ *mostly predictable*
  - Plasma protein binding interactions may be relevant to highly protein bound AEDs (PHT or VPA), but usually of little clinical significance
- Managed by dosage adjustments being guided by clinical observation and drug level monitoring
- By definition, they do not improve the therapeutic index of the individual drugs

Drug Interactions: Effect on Cytochrome P450



Landmark CJ, Patsalos PN. *Expert Rev Neurother* 2010;10:119–140; Perucca E. *Br J Clin Pharmacol* 2006 61:246–255

Pharmocokinetic Interactions Between AEDs

(Patsalos PN, Clin Pharmacokinet 2013; 52:927-966)

III. Rational Approach for AEDs Combination
2. Pharmacodynamic Interaction

- Related to interactions involving **Mechanisms of Action(MOA)**
- Additive, Supra-additive and Infra-additive in either therapeutic or adverse effect profiles
- The therapeutic index($TI = TD_{50}/ED_{50}$) of combination may be changed from the TI of the individual drugs
- Difficult to Assess
  - Animal experiments are time consuming, and their extrapolation to the clinic unclear
  - Isobolographic analysis
  - Protective index measurement in specific Sz model
  - Clinical testing, no ideal trial designs yet applied

2. Pharmacodynamic Interaction

(1) Animal Experiments

(a) Comparison of TI of individual AEDs between monotherapy and combination therapy in various animal models

Table 1. Effects of anticonvulsants administered alone and in combination with LEV in the mouse audiogenic seizure model

Name of the compound	Pretreatment time[a] (min)	ED_{50A} (mg/kg)[b] VEH plus Compound	ED_{50B} (mg/kg)[c] LEV[d] plus Compound	Change in potency ED_{50A}/ED_{50B}
Valproate	30	121 (110–144)	4.3 (1.8–9.7)	28[e]
Clonazepam	30	0.036 (0.033–0.039)	0.0016 (0.0007–0.0031)	23[e]
Diazepam	30	0.33 (0.31–0.35)	0.017 (0.0004–0.8)	19[f]
NBQX	15	27.9 (18.6–41.7)	1.5 (0.68–3.31)	19[f]
MK-801	30	0.17 (0.15–0.2)	0.01 (0.0004–0.28)	17[f]
Phenobarbital	30	9.6 (6.8–12.1)	0.6 (0.2–1.3)	16[f]
Chlordiazepoxide	30	2.9 (2.2–3.8)	0.18 (0.11–0.31)	16[f]
Bretazenil	30	0.19 (0.17–0.21)	0.017 (0.008–0.012)	11[f]
NO-711	30	2.5 (2.1–3.1)	0.5 (0.22–1.22)	5[f]
Lamotrigine	30	16.8 (14.3–19.7)	4.1 (2.0–8.7)	4.1[f]
Allopregnanolone	10	6.3 (5.8–6.9)	1.7 (0.9–5.5)	3.7[f]
Carbamazepine	30	21.2 (13.3–28.4)	5.9 (3.9–8.1)	3.6[e]
Vigabatrin	240	1367 (1331–1404)	490 (409–587)	2.8[f]
Phenytoin	30	25.7 (19.6–32.8)	13.2 (9.3–16.5)	1.9[e]
Propranolol	30	19.9 (18.5–21.5)	11.6 (9.8–13.6)	1.7[f]
Flunarizine	60	132 (118–147)	77.5 (48.1–124.7)	1.7[f]

Audiogenic seizures were induced in genetically sound susceptible mice (Animal Husbandry Unit, UCB, Belgium) with 90-dB, 10- to 20-kHz acoustic stimulus applied for 30 s. Each experimental group consisted of 10 mice that responded positively in the preselection testing performed 24 h before the experiment.
[a]All compounds were administered i.p.
[b]ED50A, dose of an anticonvulsant that was required to protect 50% animals against clonic seizures induced by audiogenic stimulation; 95% confidence intervals in parenthesis.
[c]ED50B, dose of an anticonvulsant in combination with levetiracetam that was required to protect 50% animals against clonic seizures induced by audiogenic stimulation; 95% confidence intervals in parenthesis.
[d]Levetiracetam (LEV) was administered at the dose of 5.5 mg/kg i.p. 60 min prior to testing.
[e]Reported only in the abstract form (Matagne et al., 2001).
[f]Previously unpublished.

Kaminski et al., Epilepsia 2009;50:387-397

2. Pharmacodynamic Interaction

(1) Animal Experiments

(b) Isobolographic Analysis

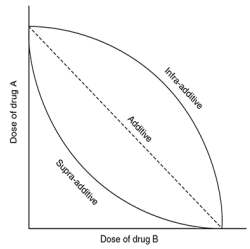


Fig. 1. Hypothetical isobologram showing the doses of two drugs required to produce a specified effect (either efficacy or toxicity) where the drugs have additive, supra-additive (synergistic), or infra-additive (antagonistic) effects.

Table I. Theoretical interactions between two drugs[a,b]

Efficacy	Toxicity
Infra-additive	Infra-additive
Infra-additive	Additive
Infra-additive	Supra-additive
Additive	Infra-additive
Additive	Additive
Additive	Supra-additive
Supra-additive	Infra-additive
Supra-additive	Additive
Supra-additive	Supra-additive

a Pure 'additive' implies absence of a positive interaction.

b The ideal interaction would be supra-additive for efficacy but infra-additive for toxicity.

Kaminski et al., Epilepsia 2009;50:387-397

Effects of AED Combinations Evaluated with Isobolography in Mice

(Lason et al. – Phamacological Reports,2011;63:271-292)

Drug A	Drug B					
	LTG	OXC	TGB	TPM	VGB	VPA
CBZ	Ant^{Add}	Add^{Add}	Add^{NE}	S^{NE}	NE	NE
GBP	S*	S^{0}	S^{Add}	S^{Add}	S^{0}	S^{Add}
LEV	Add^{0}	S^{0}	NE	S^{0}	NE	Add^{0}
OXC	Ant^{Syn}	-	Add^{Add}	S^{Add}	NE	Add^{Add}
TGB	Add^{Ne}	Add^{An}	-	Add^{NE}	S^{Add}	Add^{Ne}
TPM	S^{An}	S^{Add}	Add^{Ne}	-	NE	NE
VPA	S^{An}	Add^{Add}	S^{Ne}	NE	Add^{0}	-

Ant – Antagonism; S – synergy; Add – additivity; * – the increased level of GBP in brain has been observed; o– no neurotoxicity observed for antiepileptics at the fixed dose ratio of 1:1, recorded in the chimney test or passive avoidance task; Add– additive neurotoxicity in the chimney test calculated by isobolography; An – antagonistic neurotoxicity; Syn– synergistic neurotoxicity; CBZ – carbamazepine; GBP – gabapentin; LEV – levetiracetam; LTG – lamotrigine; – – no possibility of combination; – neurotoxicity not evaluated; NE – not evaluated by isobolography; OXC – oxcarbazepine; – synergistic neurotoxic effects; TGB – tiagabine; TPM – topiramate; VGB – vigabatrin; VPA – valproate

A Mechanistic Assessment of Pharmacodynamic AED Interactions in Animal Models

AEDs Combined				Outcome
Na^{+} blocker	+	Na^{+} blocker	→	Additive efficacy or antagonism
Na^{+} blocker	+	AED with multiple actions	→	Variable and unpredictable
AED with multiple actions	+	AED with multiple actions	→	Synergistic efficacy
Gabapentin	+	Any other AED	→	Synergistic efficacy
Levetiracetam	+	Other AEDs	→	Additive or synergistic efficacy

Deckers, Epilepsia 2000;41:1364-74; Czuczwar, Epilepsy Res 2002;52:15-23, Luzsczki , Epilepsia 47:10-20, 2006; Jonker, Epilepsia 2007;48:412-434; Kaminski, Epilepsia 2009

2. Pharmacodynamic Interaction
(2) Clinical Studies

- If a patient failed on one AED, theoretically it would make sense to try next a drug with a different mode of action
  - Principles of combination therapy in other illnesses, e.g., Hypertension, Cancer, DM, etc.
- Experimental Evidences indicate
  - Combining drugs with different modes of action might give additive or synergistic efficacy
  - Combining drugs with identical modes of action is expected to lead to neurotoxicity

➔ **"Mechanisms of Action"** seems to be an important consideration in the Choice of Next drug (?)

2. Pharmacodynamic Interaction

(2) Clinical Studies

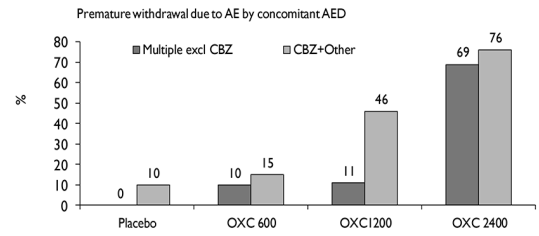
(a) ***Adverse Interactions*** in combinations of Na-channel blockers

Drug combination	Level of evidence*
Oxcarbazepine + Carbamazepine	+++
Lamotrigine + Carbamazepine	+++
Lamotrigine + Oxcarbazepine	++
Lamotrigine + Phenytoin (?)	++
Lacosamide + Na-Channel blockers	+++

* +++ Controlled trials ++ Case series studies

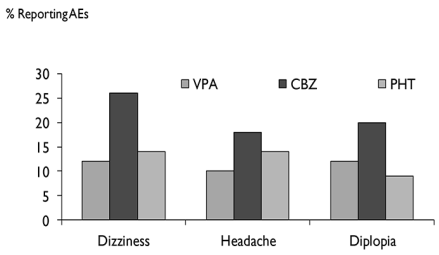
Sake et al., CNS Drugs 2010;24:1055-1068
Brodie, Epilepsy Res 1997;26:423-32; Besag, Epilepsia 1998;39:183-7; Barcs, Eilepsia 2000;41:1597-607

Oxcarbazepine Adverse Events as a Function of AED Comedication



Barcs et al Epilepsia 2000 41:1597

Lamotrigine Adverse Events as a Function of AED Comedication Data from Randomized Controlled Trials



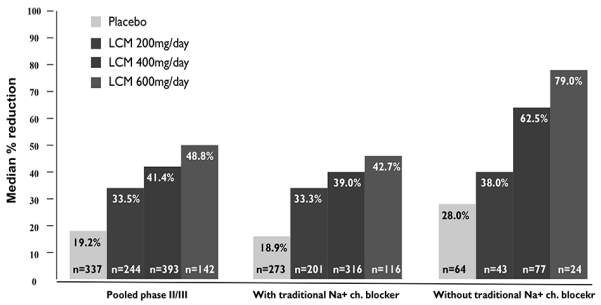
Based on Messenheimer et al Drug Safety 1998; 18:281

2. Pharmacodynamic Interactions

(2) Clinical studies

(b) Poorer efficacy in combinations of Na-channel Blockers

- Pooled analysis of phase II/III trials of LCM add-on therapy



Sake et al., CNS Drugs 2010:24:1055-1068

2. Phamacodynamic Interactions

(2) Clinical studies

(b) Poorer efficacy in combinations of Na-channel Blockers

- Rufinamide Add-on Trial (Brodie et al.,Epilepsia 2009;50:1899-1909)

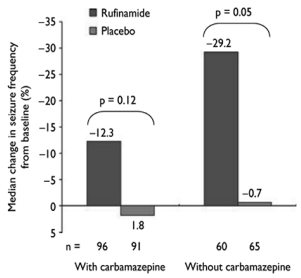


Figure
Post hoc analysis of the primary outcome measure in subjects with and without carbamazepine in their antiepileptic drug regimen.

2. Pharmacodynamic Interactions

(2) Clinical studies

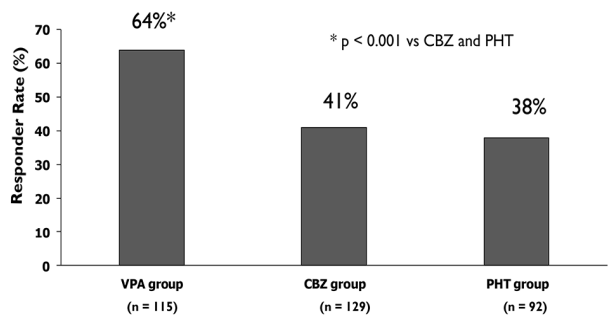
(C) Positive interactions in combinations of different mechanisms

Drug combination	Level of evidence*
Valproate + Lamotrigine	+++
Valproate + Ethosuximide	++
Phenobarbital + Phenytoin	+
Valproate + Carbamazepine	+
Carbamazepine + Vigabatrin	+
Tiagabine + Vigabatrin	+
Topiramate + Lamotrigine	+

* +++ Controlled trials ++ Case series studies + Anedoctical

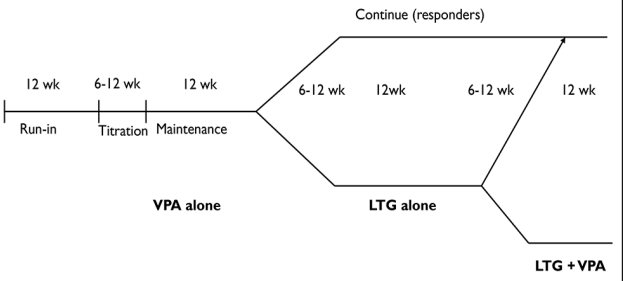
Kwan and Brodie, Drugs 2006:66:1817-29

Differences in Responder Rates to Lamotrigine as a Function of Comedication



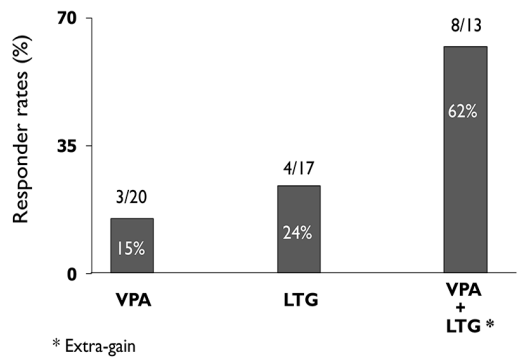
Brodie et al, Epilepsy Res.,1997; 26: 423-32

Sequential Trial of Valproate, Lamotrigine and their Combination in Partial Epilepsy



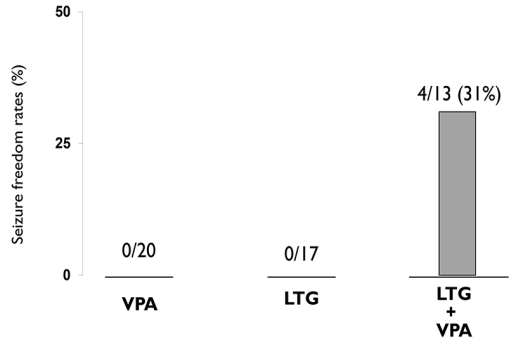
Pisani et al, Epilepsia 1999; 40:1141-6

Valproate, Lamotrigine and their Combination: 50% Responder Rates



Pisani et al, Epilepsia 1999; 40: 1141-6

Valproate, Lamotrigine and their Combination: Seizure Freedom Rates



Pisani et al, Epilepsia 1999; 40: 1141-6

Combination of VPA, LTG, and BDZ on Epileptic Drop Attacks

(Machado et al., Epilepsia 2011;52:1303-1310)

- N=32: An open-label trial in patients with refractory drop attacks(LGS in 7)
  - Frequency of drop attacks were compared at 3-month interval with the baseline period until the follow up of 12 months.
  - 4 patients were withdrawn from the study during the first 3 mo(3; skin rash, 1; f/u loss)
    - remaining 28 patients completed 12 months of treatment
- **Results**
  - **Mean dose of** VPA(35.9mg/kg/day), LTG(4/9mg/kg/day), clobazam(0.45mg/kg/day) or clonazepam(0.05mg/kg/day)
  - Reduction of drop attacks by 96%(!): 15(47%) patients free of drop attacks
    7(21%) ≥75%, 5(18%): 50% to 74%

AED combination	No.	SFR average	CI	p
CBZ	66	1.06	0.82-1.37	0.66
CBZ/VPA	54	1.08	0.83-1.40	0.56
VPA	50	1.20	0.91-1.59	0.18
VPA/PHT	41	1.10	0.85-1.41	0.47
LTG/VPA	40	0.52	0.40-0.66	3×10^{-8}
CBZ/PHT	38	1.20	0.88-1.64	0.24
PHT	33	1.21	0.81-1.80	0.34
LTG	30	0.76	0.50-1.17	0.20
LTG/CBZ	28	1.25	0.90-1.73	0.18
LTG/PHT	20	0.99	0.76-1.29	0.94
VPA/GBP	18	1.40	0.93-2.12	0.10
LTG/TPM	16	1.06	0.75-1.49	0.74
LTG/LEV	15	0.77	0.33-1.78	0.51
CBZ/TPM	15	0.53	0.26-1.08	0.08
LTG/VPA/TPM	13	0.46	0.20-1.06	0.07
LTG/VPA/PHT	11	0.98	0.71-1.37	0.91
VPA/TPM	11	0.81	0.46-1.42	0.42
CBZ/VPA/PHT	11	1.02	0.54-1.93	0.93
PHT/GBP	10	1.04	0.53-2.05	0.90
LTG/VPA/LEV	9	0.66	0.34-1.26	0.18
CBZ/GBP	9	0.92	0.36-2.34	0.85
LTG/VPA/GBP	9	0.76	0.48-1.20	0.20
LTG/TPM/LEV	9	1.15	0.63-2.10	0.60
TPM/PHT	8	0.79	0.35-1.79	0.52
TPM	7	1.44	0.84-2.46	0.15
VPA/LEV	7	0.71	0.38-1.31	0.22
LTG/CBZ/PHT	7	0.91	0.48-1.74	0.74
LTG/ZNS	6	0.93	0.78-1.11	0.32
CBZ/LEV	5	1.19	0.42-3.40	0.67
CBZ/PHT/GBP	5	2.09	0.79-5.49	0.10
TPM/LEV	5	0.64	0.30-1.38	0.18
LTG/CBZ/VPA	5	1.42	0.47-4.23	0.43

Comparative Efficacy of Combination Therapy

(Poolos et al., Neurology 2012;78: 62-68)

- 148 pts cared in 2 state hospitals
- Analysis of an average of 140 mo (± 5.8mo) of epilepsy treatment data per patient
- Mean baseline Sz Freq: 3.2/mo, exposure to a median of 4 different combinations
- Among 32 frequently used AED combinations only LTG + VPA combination had superior efficacy(p=0.00003)
- Triple drug combination did not show any significant improvement compared to duotherapy

IV. Rational Approach for AEDs Combination - Summary -

- No Class I & II evidence supporting the "Concept of Rational Polytherapy" yet
- However
  - Experimental evidence have provided the "Concept of Mechanistic Combinations"
  - Clinical evidence for "Rational Polytherapy" coincides with animal experiment, at least partly
    - Combination of drugs having same mechanisms (e.g., sodium channel blockers) is associated higher rate of AEs and lower efficacy
    - Clinical experience of mechanistic combinations are generally favorable, among which LTG + VPA combination has the best clinical data of synergism
- "Concept of Rational Polytherapy" is still an Art than Science, but the best Guideline for pharmacotherapy of DREs at present