
بسم الله الرحمن الرحيم

Rational polytherapy

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introduction

- ✓ Epilepsy is one of the most common neurological diseases, affecting about 65 million people in the world .
- ✓ The incidence range is 40-190 per 100.000 people per year, with a pick of incidence in low-income countries.
- ✓
- ✓ 30% develop a drug-resistant epilepsy

Would Sherlock Holmes agree with our definition of rational polytherapy?

rational polytherapy : identify AEDs combinations that maximize efficacy and minimize side effects

- ✓ Antiepileptic polytherapy may be indicated in patients experiencing drug resistant epilepsy.

- ✓ To date, there are no evidence-based criteria on how to combine different antiepileptic drugs (AEDs) together, in order to obtain the best therapeutic response

drug-resistant epilepsy

DRE is defined after the “failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom”.

The latter may last either 1 year or three times the longest inter-seizure interval reported

- ✓ As the number of AEDs rapidly increases, the number of combination regimens has increased exponentially. with 25 currently recognized AEDs, 300 combinations are possible for duotherapy and several thousands for triple drug therapy.

- ✓ analysis of relevant clinical features and logical synthesis of orders or priorities by knowledgeable and experienced epileptologists

- ✓ This is the reason why the ILAE-Task Force recommends the referral of patients to dedicated epilepsy centers if they fail to show adequate response in trials of the first two AED

newly diagnosed patients with epilepsy are initially treated with AED monotherapy.

50% of patients with untreated epilepsy, achieve seizures control with the first monotherapy .

when the first antiepileptic drug monotherapy fails, the second-line AED should be tried as an alternative monotherapy, while polytherapy should be considered only after the failure of at least two monotherapies .

other authors recommend 3 trials of monotherapy before switching to polytherapy

The success rates of drug trials after failure of the first two drugs were significantly lower but were not different among subsequent drug regimens, ranging from 12.5% to 22.2%. Therefore, the first and second drug trials are likely to be the major determinants of therapeutic outcomes of epilepsy and support the International League Against Epilepsy (ILAE)

AEs are determined more by individual susceptibility, type of AEDs used, and physician skill than the number of AEDs. Therefore, the previous assumption of monotherapy being associated with fewer AEs than polytherapy is probably not tenable anymore in the era of new AEDs.

Several factors must be considered for an adequate anticonvulsant drugs combination such as:

epilepsy type, patient history, patient preference, pregnancy, comorbid conditions, concomitant drugs, previous AEDs used and potential adverse effect profile .

There are no approved criteria for selecting the most appropriate combination of AEDs; therefore, this is often guided by the clinical experience rather than evidence-based medicine

interactions between AEDs in terms of synergy (supra-additivity), additivity, antagonism (infra-additivity)

- ✓ When the efficacy of the drug combination is equal to the sum of the individual drug efficacies, the interaction is defined as “additive”
- ✓ When the efficacy of the two drugs administered in combination is greater than the expected efficacies of the single drugs taken separately, the interaction is presumed to be “supra-additive”
- ✓ When the global efficacy is smaller than the sum of individual drug efficacies, the interaction is considered as “infra-additive”

Drug combination	Level of evidence
Valproate and lamotrigine[25-29]	+++
Valproate and ethosuximide[30]	++
Lamotrigine and topiramate[31]	+
Lacosamide and levetiracetam[32,33]	++
Lamotrigine and levetiracetam[35,36]	++
Valproate and levetiracetam[34]	+
Valproate, clobazam and stiripentol[37]	+++
Valproate, lamotrigine and benzodiazepine[38]	++

Infra - additive

CBZ + PB

CBZ + PHT

Drug interactions need to be assessed even from the tolerability profile

Indeed, the most favorable combinations would be those characterized by an anticonvulsant supra-additive effect and, possibly, a neurotoxic antagonism.

Acceptable combinations could be also considered those featured by anticonvulsant synergy and neurotoxic additivity or anticonvulsant additivity and neurotoxic infra-additivity .

Although this approach has been extensively used in experimental models, its applicability to humans is challenging because of the inter-individual variation in the pharmacokinetic profile .

Anyway, when the first two AEDs are not able to induce an optimal response, polytherapy should be considered, especially in case of high frequency seizures and underlying disease

Combination strategy consists of testing polytherapies in order to find that one which best fits to the patient, in terms of efficacy and tolerability.

The addition of a fourth drug should be generally avoided, considering that the use of more than three AEDs tends to deeply reduce the safety and tolerability, due to the occurrence of adverse events (AEs) and a scarce improvement in seizure control .

When an acceptable seizure control is not achieved, neurosurgery treatment should be recommended.

If resective surgery is not feasible, palliative surgery or repetitive neurostimulation systems (including vagus nerve, trigeminal nerve, or deep brain stimulation) can be considered .

POINTS

older AEDs can be responsible for many interactions, among themselves as well as with other medications, due to their effect on the hepatic cytochrome P450

trying to avoid associations of AEDs with similar AEs profile

Co-medication may increase the risk of idiosyncratic reactions : for example, valproate/lamotrigine combination augments the probability of lamotrigine-induced hypersensitivity

enzyme-inducing AEDs/valproate associations increase the risk of pancreatitis, hyperammonaemia, hepatotoxicity and encephalopathy

when managing valproate/lamotrigine combination is the development of tremor. In fact, postural and action tremor can be caused by either each drug or a summary effect of the combination of the two AED

Generally, recommended dosing regimens for lamotrigine when used in combination with valproate are halves doses.

points

Phenobarbital, phenytoin and carbamazepine belong to first generation AEDs. They induce the metabolism of liposoluble drugs such as oral anticoagulants, antiretrovirals immunosuppressants, antiarrhythmics and oral contraceptives.

There are several chronic adverse effects caused by enzyme induction such as sexual dysfunction, reduced bone density, changes in cholesterol concentration and other cardiovascular effects

Carbamazepine, lamotrigine, ethosuximide, phenytoin and phenobarbital should be avoided in patients with hematological disorders since they can cause bone marrow suppression

Pregabalin, gabapentin, vigabatrin and valproate may lead to an increase in body weight and therefore, should be avoided in obese or diabetic subjects

points

Topiramate and zonisamide increase the risk of anorexia and, therefore, should not be used and given together in underweight patients . they are also not indicated in patients with nephrolithiasis due to the increased risk of kidney stones

Topiramate, zonisamide and levetiracetam cannot be used in psychiatric patients because they can worsen anxiety, depression, emotional lability and psychosis . Lacosamide, rufinamide and retigabine should not be prescribed in patients with long QT syndrome or in people taking drugs that increase QT .

points

- ✓ Patients with epilepsy suffering from migraine may benefit from the administration of topiramate or valproate

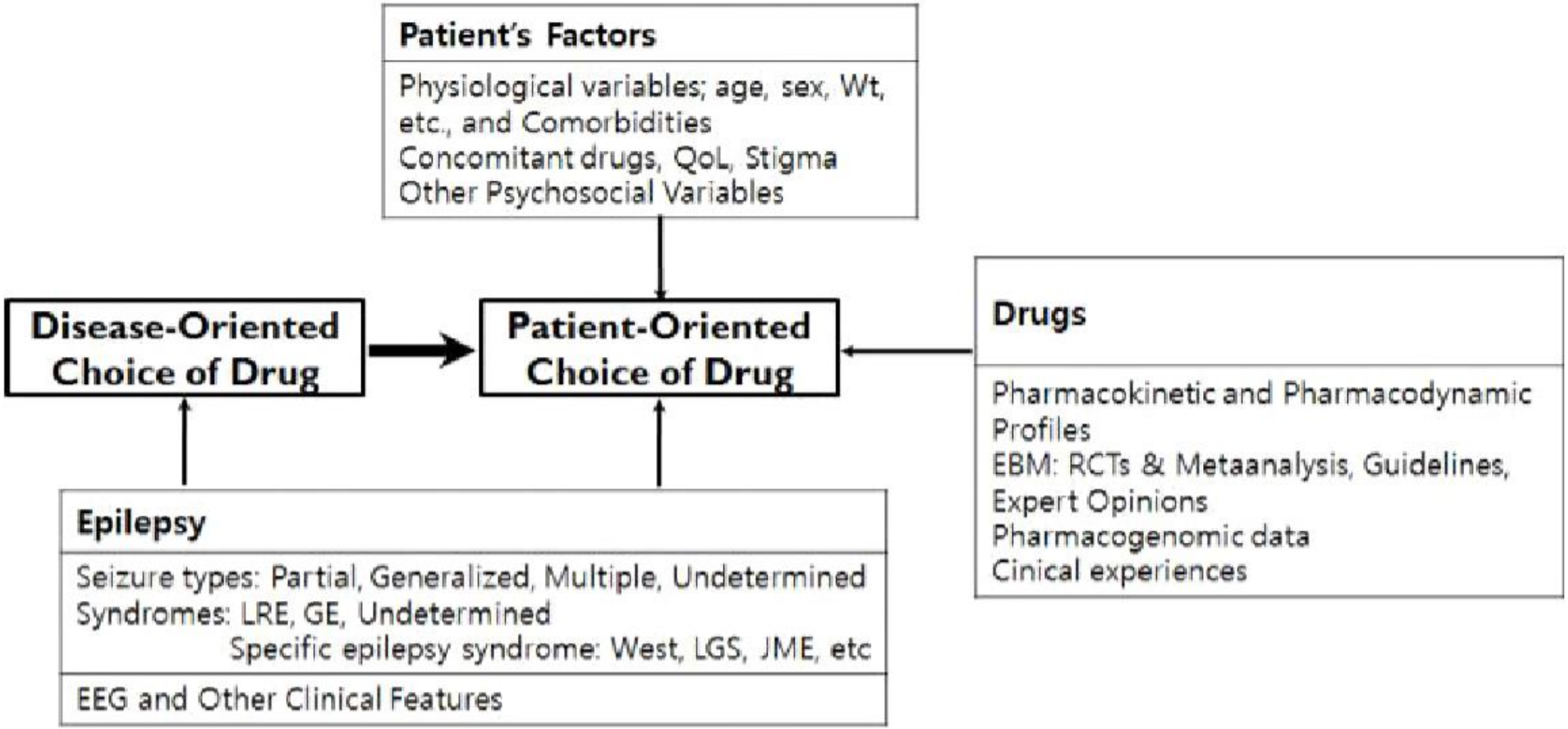
- ✓ Patients with generalized anxiety disorder or neuropathic pain and focal-onset seizures may benefit from therapy with pregabalin or gabapentin

- ✓ **Polytherapy in elderly** :regiments for this subgroup of patients might be challenging for the high prevalence of comorbidities and the chronic use of concomitant medications. Therefore, due to altered pharmacokinetics and a higher susceptibility to develop AEs, AEDs polytherapy in elderly should be chosen with caution

- ✓ In the next future, a deeper knowledge genetics of epilepsy will probably lead to therapies based on **precision medicine** and not on empirical evidence.

Practical advices for the rational polytherapy

- ✓ Start therapy with a single AED, choosing the right drug based on the seizure type, epileptic syndrome and the patient characteristics, such as age, sex, comorbidity, comedications and physical conditions
- ✓ Find the correct dose of the first line AED, increasing the dose gradually and steadily to avoid poor tolerance
- ✓ Replace the first AED with another in case of adverse and/or idiosyncratic effects already in small doses
- ✓ Associate AEDs with different mechanisms of action
- ✓ Avoid the combination of AEDs with a similar spectrum of adverse effects
- ✓ Confirm the correct diagnosis of epilepsy, the type of seizure and the epileptic syndrome and compliance to patient care, before changing the combination of AEDs for insufficient response to therapy
- ✓ Test different duotherapies before adding a third drug
- ✓ Switch to triple therapy in case of suboptimal seizure control
- ✓ Avoid the association of 4 or more AEDs, because the combination with more than 2 drugs increases the risk of negative side effects and pharmacokinetic interactions especially in elderly patients who take many medications


Patient's Factors
Physiological variables; age, sex, Wt, etc., and Comorbidities
Concomitant drugs, QoL, Stigma
Other Psychosocial Variables
Disease-Oriented Choice of Drug
Patient-Oriented Choice of Drug
Drugs
Pharmacokinetic and Pharmacodynamic Profiles
EBM: RCTs & Metaanalysis, Guidelines, Expert Opinions
Pharmacogenomic data
Cinical experiences
Epilepsy
Seizure types: Partial, Generalized, Multiple, Undetermined
Syndromes: LRE, GE, Undetermined
Specific epilepsy syndrome: West, LGS, JME, etc
EEG and Other Clinical Features

Step 1	Step 2
Candidate drugs of preference	Drugs matching the partner drug
Drugs with no previous exposure	Drugs with different MOAs
Drugs proven effective, at least partially, in previous exposure	Drugs with no or low potential of pharmacokinetic interactions
Drugs with desirable MOAs	Drugs showing different side effect profiles
Non-enzyme-inducing drugs or drugs showing no or low risk of pharmacokinetic interactions with concomitant drugs	Drugs known to have synergistic interactions in combination
Drugs effective for the patient's comorbidities or at least not deleterious to the comorbidities	
Drugs with a high therapeutic index or good tolerability profile	

Table 4. Choice of antiepileptic drugs related to comorbidities

	Choose	Avoid
Obesity ± DM	TPM, ZNS	VPA, PGB, GBP, PER
Migraine	TPM, VPA, ZNS, PBG, GBP	
Skin rash	LEV, GBP, PGB, TPM, VPA, PER, LCM	LTG, OXC, CBZ, PHT, PB
Neuropathic pain	PGB, GBP, CBZ, OXC, PHT	
Depression ± Behav/Psych	LTG, CBZ, OXC, VPA, PGB	LEV, PB, PRM, TPM, ZNS, PER
Cognitive dysfunction	LTG, LEV, OXC	PB, TPM, ZNS
Concomitant drugs	GBP, LEV, PGB, VPA	EI-drugs
Restless legs syndrome	GBP, PGB, CZP	
Renal stone		TPM, ZNS
Glaucoma		TPM
Hematological disorder		CBZ, VPA
Hyponatremia		OXC, ESL, CBZ
Hepatic disease	New AEDs (not hepatic toxic, renal excretion)	VPA
Renal disease	Old AEDs (excreted by hepatic metabolism)	
Osteoporosis	LTG, LEV	EI-drugs, TPM, VPA, ZNS
Gait disturbances		CBZ, PHT, PER
Tremor	TPM, PER	VPA
Parkinson disease	ZNS	
Cardiac arrhythmia		CBZ, LTG, LCM, and others SCB
Cancer	VPA, LEV, PER	EI-drugs
Heat stroke		TPM, ZNS
Atherosclerosis		EI- drugs

Modified from reference 55 with permission.
DM, diabetes mellitus; TPM, topiramate; ZNS, zonisamide; VPA, valproic acid; PGB, pregabalin; GBP, gabapentin; PER, perampanel; LEV, levetiracetam; LCM, lacosamide; LTG, lamotrigine; OXC, oxcarbazepine; CBZ, carbamazepine; PHT, phenytoin; PB, 약어풀이; Behav/Psych, behavioral and/or psychiatric disorders; PRM, primidone; EI-drug, enzyme-inducing drugs; CZP, clonazepam; ESL, eslicarbazepine; AED, antiepileptic drug; SCB, sodium-channel blockers.