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Review article

Clinical opinion: Earlier employment of polytherapy in sequential pharmacotherapy of epilepsy

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ABSTRACT

Modern pharmacotherapy for epilepsy consists of orderly, sequential drug trials, in which antiepileptic drugs (AEDs) are chosen under the concept of individual patient-oriented (or - tailored) pharmacotherapy. Although monotherapy has been established as the preferred mode of AEDs therapy in both newly diagnosed and drug resistant epilepsies, there are still lack of evidence to favor either monotherapy or polytherapy in epilepsy, which has generated continuing controversies on the preferred mode of pharmacotherapy. However, each mode of pharmacotherapy may have both advantages and disadvantages, which are different and variable related to individual case scenario.

We conducted a brief comparative overview between monotherapy and polytherapy to provide clues for earlier employment of polytherapy in each steps of sequential drug trials. Previous claims about the advantages of monotherapy over polytherapy are not supported but gradually losing its ground by the introduction of a large number of drugs carrying pharmacological advantages for combination therapy. Current evidence stresses the importance of combining drugs having synergistic interactions for better outcome of polytherapy, which has not been considered in previous clinical investigations comparing monotherapy and polytherapy. It is likely that a significant improvement in the outcome of current AEDs therapy is feasible by earlier employment of polytherapy as well as identification of combination drug regimens carrying synergistic interactions. At present, lamotrigine(LTG) and valproate(VPA) combination regimen is the only well documented synergistic regimen, but there are a long-list of candidate regimens requiring future trials in appropriate designs.

1. Introduction

Since the introduction of Bromide in 1857, numerous compounds have been marketed for pharmacotherapy of epilepsy but many of them were withdrawn due to either unacceptable adverse effects (AEs) or insufficient efficacy (Shorvon, 2009a, 2009b). A few drugs including phenytoin (PHT), phenobarbital (PB), carbamazepine (CBZ) and valproate (VPA), have remained in the market for their continuous use and underwent comparative monotherapy trials in patients with newly diagnosed epilepsy, which have promoted CBZ and PHT as first-line drugs for focal seizures (FS) and VPA as the broad-spectrum drug being effective for both generalized seizures (GS) and FS (Mattson et al., 1985,1992; Heller et al., 1995; de Silva et al., 1996). Ethosuximide (ESM) was introduced in 1958 and still the choice of drug in absence epilepsy (Glauser et al., 2010). Benzodiazepine derivatives are broad-spectrum AEDs being used in both FS and GS, however, they are considered second-line drugs being useful in adjunctive therapy, which may be related to their sedating side effects and potential tachyphylaxis (Callaghan and Goggin, 1988; Specht et al., 1989; Canadian Clobazam Cooperative Group, 1991). Since introduction of CBZ and VPA in late 1960's, which were major drugs during the era of conventional drug, there was a long hibernation period in the new drug development for epilepsy until the marketing approval of vigabatrin (VGB) in UK and zonisamide (ZNS) in Japan in 1989 (Sander et al., 1990; Yagi and Seino, 1992), which opened the "Era of New AEDs" (Allen, 1995). Seventeen new drugs have been introduced to the market until now and we have at least 25 AEDs, including both conventional and new AEDs, to use in our practice, which is completely a different environment for

Abbreviations: AE, adverse effect; AEDs, antiepileptic drugs; EI-AED, enzyme inducingantiepileptic drug; FS, focal seizures; GS, generalized seizures; GTCS, generalized tonic-clonic seizures; ITD, initial target dose; MOA, mechanism of action; MTD, maximally tolerable dose; QOL, quality of life; RCT, randomized clinical trial; TDL, total drug load; SFR, seizure free rate; SRES, surgically remediable epilepsy syndromes

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pharmacotherapy of epilepsy from the era of conventional AEDs (Santulli et al., 2016; Shih et al., 2017).

The impact of new AEDs on epilepsy management has been significant to change the paradigm of pharmacotherapy as follows. Firstly, new drugs underwent rigorous randomized controlled clinical trials (RCTs) as add-on therapy in patients with drug resistant epilepsy (DRE) and then, after a few years of successful performance as adjunctive drugs for patients with DRE, they underwent RCTs of initial monotherapy in patients with newly diagnosed FS and generalized tonic-clonic seizures (GTCS) for approval as first-line drugs (Kwan and Brodie, 2003; Perucca, 2012). Also, new AEDs underwent a variety of postmarketing clinical trials aiming at further evaluation of their long-term outcomes as well as expansion of clinical indications beyond the limit of defined indications at the time of marketing approval (Sander, 2005; Zaccara et al., 2006). These clinical development programs of new AEDs have firmly established the practice of "Evidence-based-Medicine (EBM)" in pharmacotherapy of epilepsy by providing extensive database of different hierarchies of evidence (Jenicek, 2006). Most new AEDs have been subjected to a systemic review and meta-analysis, which were adopted to the "Clinical Practice Guidelines", which were published by many authoritative institutions (French et al., 2004a, 2004b; Payakachat et al., 2006; Nunes et al., 2012). Secondly, new AEDs are characterized by better pharmacokinetic profiles including less drug interactions, diverse mechanisms of action (MOA), and better tolerability profiles, which are important advantages for polytherapy (Perucca, 1996). Widely available new AEDs and their EBM data from RCTs of add-on therapy encouraged physicians to practice polytherapy including new AEDs in the regimen for patients who failed to monotherapy, which has slowly revived polytherapy in real world practice (Deckers, 2002; French and Faught, 2009; Brigo et al., 2013). Thirdly, diversities of new AEDs in terms of MOA, adverse effects (AEs) and therapeutic profiles including their efficacy in various non-epileptic conditions, in conjunction with a rapid progress in a broad spectrum of clinical epileptology have precipitated the paradigm shift of pharmacotherapy, from "Disease (seizure types and epilepsy syndromes)-oriented Pharmacotherapy" to "Patient-oriented (or -tailored) Pharmacotherapy" (Perucca, 2003). The choice of appropriate drugs has been exercised on the basis of multi-dimensional assessment of epilepsy, candidate AEDs, and individual patient's conditions including demographic and physiological conditions, comorbidities, and psychosocial environment (Fig. 1). The concept of patient-oriented pharmacotherapy expanded the goal of pharmacotherapy also from "no seizure and no side effects" to "free of burden from physical, psychological and social consequences of epilepsy" (Kerr, 2012)

However, despite major advances in pharmacotherapy and clinical epileptology over past 3 decades, there have been still continuing controversies about the optimal mode of therapy. This review is aiming at the proper positioning of polytherapy in serial steps of pharmacotherapy by careful analysis of currently available evidence

2. Principles of antiepileptic drug therapy

The pathway of epilepsy management starts with an accurate diagnosis of epilepsy, seizure types, and epilepsy syndromes, which is followed by administration of systemic drug trials and appropriate diagnostic and therapeutic modalities at each step of treatment pathway (Fig. 2). Because AEDs therapy is complicated by unpredictability of efficacy and AEs, variable optimal doses to individual patient, and prolonged, sometimes life-long therapy, AED trials should be conducted in an orderly fashion consisting of initial monotherapy of first drug and following sequential trials of second, third and next drugs along with careful assessment of the patient's response at each step of pharmacotherapy (Mohanraj and Brodie, 2006). As the number of new AEDs increases and enormous amount of evidence accumulates, optimal pharmacotherapy has become more demanding to caring physicians (Santulli et al., 2016; Perucca and Tomson, 2011), who is aiming at choosing the best drug for their patients throughout the whole process of pharmacotherapy, from the initial treatment to the multiple steps of sequential drug trials. Another important issue is to select the mode of pharmacotherapy, "Monotherapy vs. Polytherapy", for optimal outcome of chosen drugs at each step of sequential drug trials, which has been the subject for never ending debates, primarily due to lack of evidence and great diversities in patients' response to different drug regimens (Lammers et al., 1995; Kwan and Brodie, 2006; St. Louis, 2009; Barker-Haliski et al., 2014). Apparently, the adoption of optimal mode of therapy is affected by multiple factors including clinical characteristics of individual patient and should be harmonized with given practice environment to achieve the best clinical outcome, implying a flexible approach. Dogma of monotherapy, which was established in the era of conventional AEDs may need some modification and compromise to harmonize with changing concepts of pharmacotherapy in the era of New AEDs, which may help adopt new waves to the real world practice.

2.1. Era of monotherapy

Early phase of modern pharmacotherapy was predominated by Bromide, however, it was seldom used alone but combined with many other drugs considered being effective in epilepsy (Shorvon, 2009a). A survey of patients with epilepsy from 15 medical centers in Europe in early 1970s revealed that a patient was taking three AEDs in average, reflecting polytherapy as the prevailing mode of pharmacotherapy (Guelaen et al., 1975). The application of blood level measurement of AEDs in clinical practice at 1960′s introduced the concept of therapeutic level of AEDs and established the clinical importance of pharmacokinetic drug interactions, which have provided the theoretical basis of Monotherapy (Shorvon, 2009b). Reynolds et al. (1976) reported that a major proportion of patients who were not adequately controlled had lower blood levels of PHT and the escalation of PHT doses up to the therapeutic level has markedly improved seizure control. Thus the use of adequate dose of a single drug was considered more useful than prescribing multiple drugs together, which was supported by a series of clinical investigations (Shorvon and Reynolds, 1979; Reynolds et al., 1981; Schmidt, 1982, 1983). Schmidt and Richter (1986) also found that the conversion of polytherapy to monotherapy in patients with refractory epilepsy unresponsive to polytherapy resulted in a significant improvement of either seizure control or side effects in 34 of 59 patients to conclude that alternative monotherapy is effective and preferred to polytherapy even in patients with DREs. The concept that most patients with epilepsy do not require polytherapy has gained a global recognition to promote monotherapy as the standard mode of AEDs therapy despite lack of any head to head RCTs comparing monotherapy with polytherapy. Therefore, a series of monotherapy trials of first drug, second, third, and next drugs has become a prevailing algorithm of sequential pharmacotherapy in epilepsy.

Initial monotherapy of first drug starts with a lowest dose, which is gradually escalated up to the initial target dose (ITD) for maintenance and assessment of patients' response. If seizures recurred, its dosage is further escalated to the moderate dose and then until the patient become seizure free or develops side effects, which is called monotherapy of maximally tolerable dose (MTD). If the first drug monotherapy failed to achieve satisfactory seizure control at MTD, a second drug is introduced in a similar manner of "start low and slow escalation", while the first drug is gradually tapered off to achieve the substitution monotherapy of second drug. If second drug monotherapy failed again, it satisfies the ILAE definition of DRE and the etiology of DRE must be re-assessed; a progressive lesion must be excluded and non-compliance or other causes of pseudo-refractory epilepsy should be ruled out. Video-EEG recording and advanced neuroimaging studies may be indicated in patients requiring a diagnostic precision (Fig. 2). If the patient has a surgically remediable epilepsy syndrome (SRES), referral for a timely surgery should be discussed with the patient. If the patient

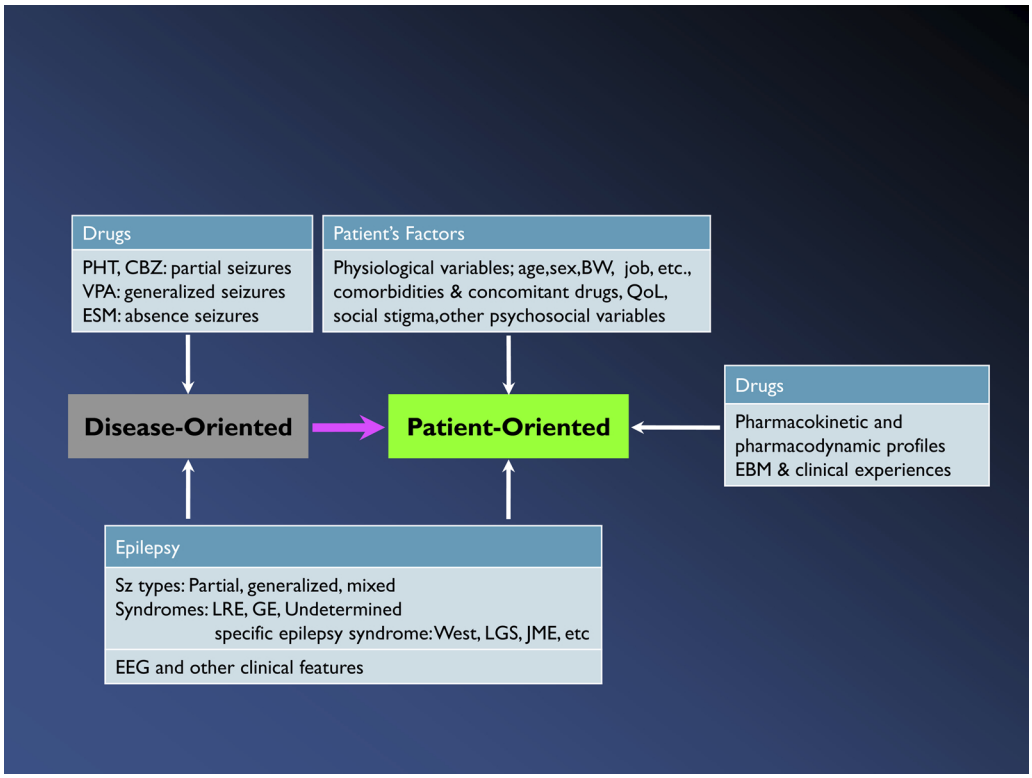

Fig. 1. Patient- oriented (or -tailored) Choice of Antiepileptic Drugs(AEDs).
Concept for the choice of antiepileptic drugs(AEDs) have changed from the "disease-oriented" in the past to the "Patient-oriented" choice of drugs in the era of new AEDs, which requires comprehensive assessment of (1) Disease factors (diagnosis of seizure types and epilepsy syndromes, severity and frequencies, etc.), (2) Drugs (pharmacokinetic and pharmacodynamic profiles, EBM data, adverse effects and tolerability, etc.), and (3) Patients' condition (age, sex, job, physiological condition, intelligence, comorbidities, concomitant drugs, etc.) Choosing the AED best fitting to these multi-dimensional assessment is the standard practice.
CBZ; carbamazepine, ESM; ethosuximide, PHT; phenytoin, VPA; valproate, BW; body weight, EBM; evidence-based medicine, EEG; electroencephalography, GE: generalized epilepsy, JME; juvenile myoclonic epilepsy, LGS; Lennox-Gastaut syndrome, LRE: localization-related epilepsy, QOL; quality of life.

does not have a SRES and truly drug-resistant, further drug trials are the mainstay of further management, either in substitution monotherapy or combination therapy (Shorvon, 2000; Kwan and Sperling, 2009; St. Louis et al., 2009). If the third drug monotherapy failed again, most epileptologists may expect a poor outcome from further monotherapy trials to undergo polytherapy (Bourgeois, 2000a,b; Shih et al., 2017). Difficulties associated with substitution monotherapies after the failure of first drug monotherapy are often encountered during the process of withdrawing the failed drug in relation to the introduction of newly chosen drug. The speed and duration of drug withdrawal, dose escalation of the newly introducing drug, and risk assessment or measures to avoid seizure worsening related to drug switch are not clearly defined but largely depend on skills and experiences of caring physicians. In fact, previous studies have shown that a proportion of patients who were transferred from combination therapy to substitution monotherapy showed decreased efficacy resulting in higher rate of seizure recurrences (Brodie and Yuen, 1997; Brodie and Mumford et al., 1999), which requires a caution in the conversion to substitution monotherapy. If the failed drug was not effective and carried a low risk of withdrawal seizures, a schedule of simultaneous tapering of the failed drug along with the introduction of newly chosen drug may be undertaken (Fig. 3A). If the scenario was different, the failed drug is at least partially effective and carries high risk of withdrawal seizures and the patient is risk-averse, the tapering of the first drug is postponed until the second drug is reached at its ITD (Fig. 3B). Apparently, the major concept of serial trials of substitution monotherapy is to avoid the risk of polytherapy to achieve the advantages of monotherapy, thus simultaneous administration of two drugs over extended period was generally not recommended for the risk of drug interactions and emergence of side effects related to higher total drug load [TDL = PDD/DDD: ratio of prescribed daily dose (PDD) to defined daily dose (DDD) of AEDs by WHO guideline].

Major AEDs in the era of conventional AEDs are either broad hepatic enzyme inducers or inhibitors, thus their combinations are liable to complex drug interactions interfering with the maintenance of adequate blood levels, precipitating emergence of various side effects affecting patients' quality of life (QOL) and compliance, and difficulties in the assessment of patients' response to individual drug (Perucca, 1996). MOAs of conventional drugs are limited in scope and often overlapping, thus they are difficult to expect any synergistic interactions from their combination but higher risks of additive neurotoxicities. Also, they have a narrow spectrum of therapeutic index, which carry a high risk of neurotoxicities from a higher TDL, a frequent companion of polytherapy (Lammers et al., 1995). With only a few number of AEDs being available, it was also considered important to accurately assess the patient's responses to individual drugs to maintain a lifelong drug treatment (Deckers et al., 2003). In the era of conventional AEDs, most epileptologists fully agreed with the adoption of monotherapy as the best chosen mode of pharmacotherapy and monotherapy has become the dogma of pharmacotherapy in epilepsy over past decades and still it is (Reynolds et al., 1976; Shih et al., 2017).

2.2. Revival of polytherapy

With introduction of 17 new AEDs to the market, we have at least 25 AEDs available to our practice, which is a completely different practice environment from the era of conventional drug consisting of only 3 to 4 major AEDs and a few second-line drugs (Santulli et al., 2016). Compared to conventional AEDs, which were introduced to the market after their demonstration of efficacy in only a few clinical series, new AEDs underwent rigorous preclinical and clinical trials under a highly organized drug development program. If conventional drugs had been used in both monotherapy and polytherapy from the time of introduction, new drugs were initially indicated as adjunctive therapy in patients with DREs, who were already taking one or more AEDs in full doses. Therefore, introduction of new AEDs was directly linked with the revival of polytherapy, which has become a major mode of pharmacotherapy in patients with DREs (Luciano and Shorvon, 2007; French and Faught, 2009; Canevini et al., 2010). New AEDs, if they performed satisfactorily as adjunctive drugs in real world practice for a few years, underwent RCTs of monotherapy to be promoted as first-line drugs in focal seizures and GTCS with some of them becoming the drug of choice

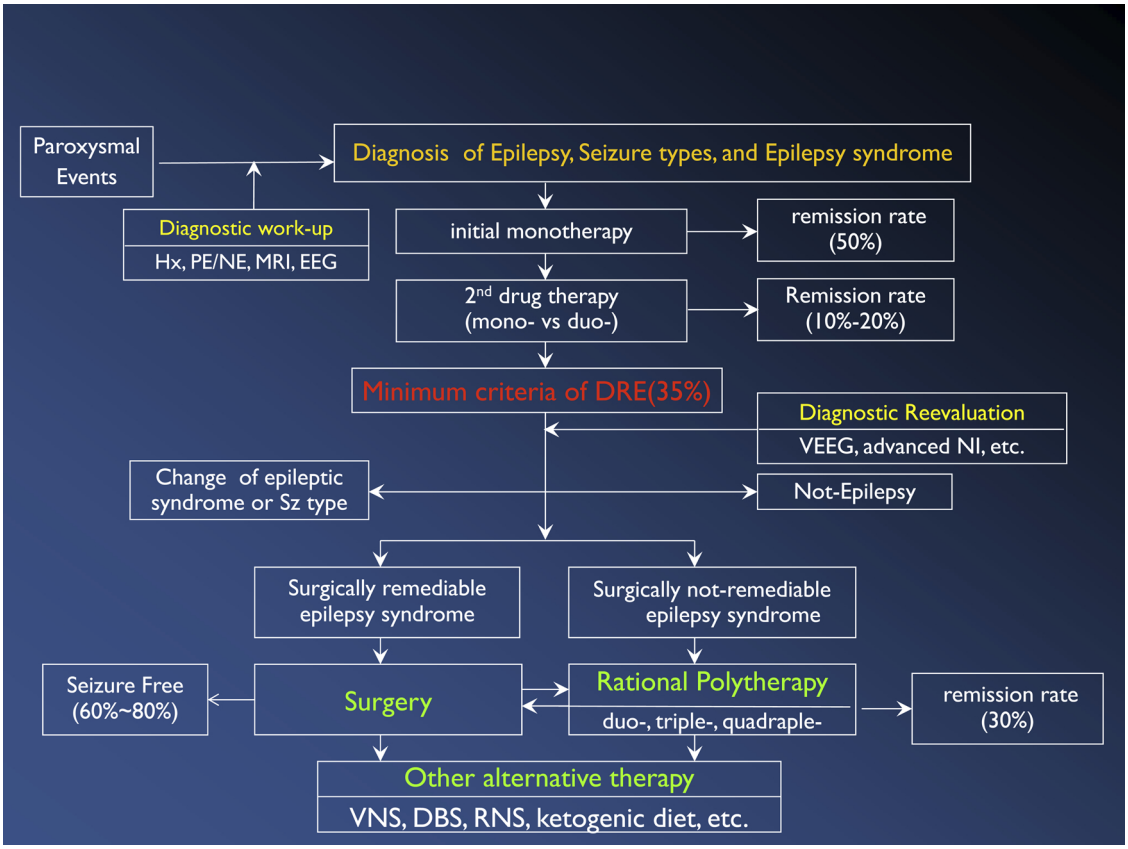

Fig. 2. Pathways of Epilepsy Management.

Epilepsy management starts with the accurate diagnosis of seizure types and epilepsy syndromes. Initial monotherapy is the standard mode of treatment resulting in 50% of prolonged seizure freedom. If initial monotherapy failed to control seizures, physicians choose a second drug for either substitution monotherapy or duotherapy with seizure free rate (SFR) of 10%–20% (or 30%–40% of patients undergoing second drug therapy), thus about 60%–70% of patients may achieve seizure freedom by first two drug trials. Failure to adequate trials of first two drugs satisfy the ILAE criteria of drug resistant epilepsies (DREs) and physicians need to re-evaluate the diagnostic precision of epilepsy to exclude the possibility of pseudo DREs and/or identify the cause of drug resistance, etiology of epilepsy, or progressive lesions. If patients were confirmed to have DREs and belong to surgically remediable epilepsy syndromes (SRES), earlier referral to epilepsy surgery may carry higher benefit-risk ratio compared continuing drug trials. If patients do not have SRES, systematic trials of 3rd, and next drug trials in various combination therapy may be required with 30% of SFR being reported. If 5th to 6th drug trials failed to control seizures, alternative therapy including VNS, DBS, or ketogenic diet therapy, or resective surgery may be considered.

Pseudo DREs include (1) wrong diagnosis (seizure types and epilepsy syndromes, non-epileptic seizures including psychogenic non-epileptic seizures, syncope, movement disorders, panic attacks or other paroxysmal symptoms), (2) wrong treatment include using wrong AEDs, which are not first-line drugs for seizure types or epilepsy syndromes or aggravating comorbidities, or wrong doses, either too low or high doses), and (3) Patient's faults may include poor drug adherence, maintenance of wrong life style, etc.

DBS; deep brain stimulation, DRE; drug-resistant epilepsy, EEG; electroencephalography, Hx; history taking, MRI; magnetic resonance imaging of brain, NI; neuroimaging PE/NE: physical and neurological examination, RNS; responsive neurostimulation, VEEG: video-EEG recording, VNS; vagal nerve stimulation.

in several specific epilepsy syndromes (Kwan and Brodie, 2003; Perucca, 2012). (Fig. 4). New AEDs passing through the rigorous drug developmental program were found to have better tolerability with higher therapeutic index, diverse MOAs, better pharmacokinetic profiles including no or less drug interactions, and less serious systemic side effects, which are desirable pharmacological profiles for polytherapy (Kwan and Brodie, 2006; Patsalos, 2013). However, extensive head to head trials of new drugs to conventional drugs in initial monotherapy for patients with newly diagnosed epilepsy failed to demonstrate any superiority of new AEDs to conventional drugs in efficacy but some advantages in tolerability, thus the impact of new AEDs on the seizure control was often not considered significant despite so intense investment devoted to the clinical development programs of new AEDs (Schmidt, 2002; Kwan and Brodie, 2003; Brodie et al., 2012; Stephen et al., 2012).

As the number of new drugs have increased linearly, the number of potential combination regimens increases exponentially. With 25 AEDs available to use, physicians are facing about three hundred potential duotherapy regimens and thousands of triple drug combination regimens, which are too many for conducting serial trials of each different drug regimens in a given patient. Therefore, among these large number of potential drug regimens, "How to choose the most desirable combination regimen?" has become an important practical issue. Kwan and Brodie (2000b), from a small scale observational study of patients who failed to the first drug monotherapy, found that the combination of a drug having sodium channel blocking effects and a drug having multiple MOAs were more effective than other combinations, which has complied with this important clinical question. All drug regimens are probably not same in either efficacy or tolerability but carrying different pharmacological interactions based upon their pharmacokinetic profiles and MOAs, thus choosing the right combination regimen for a given patient, has become an important issue for optimal pharmacotherapy, which has raised the concept of "Rational Polytherapy (St. Louis, 2009; French and Faught, 2009; Brodie and Sills, 2011)

Rational Polytherapy is a hypothesis not evidence-based but driven by theoretical considerations from preclinical experiments and clinical observations. It is focused at producing desirable pharmacodynamic drug interactions of AEDs by combining drugs having different MOAs

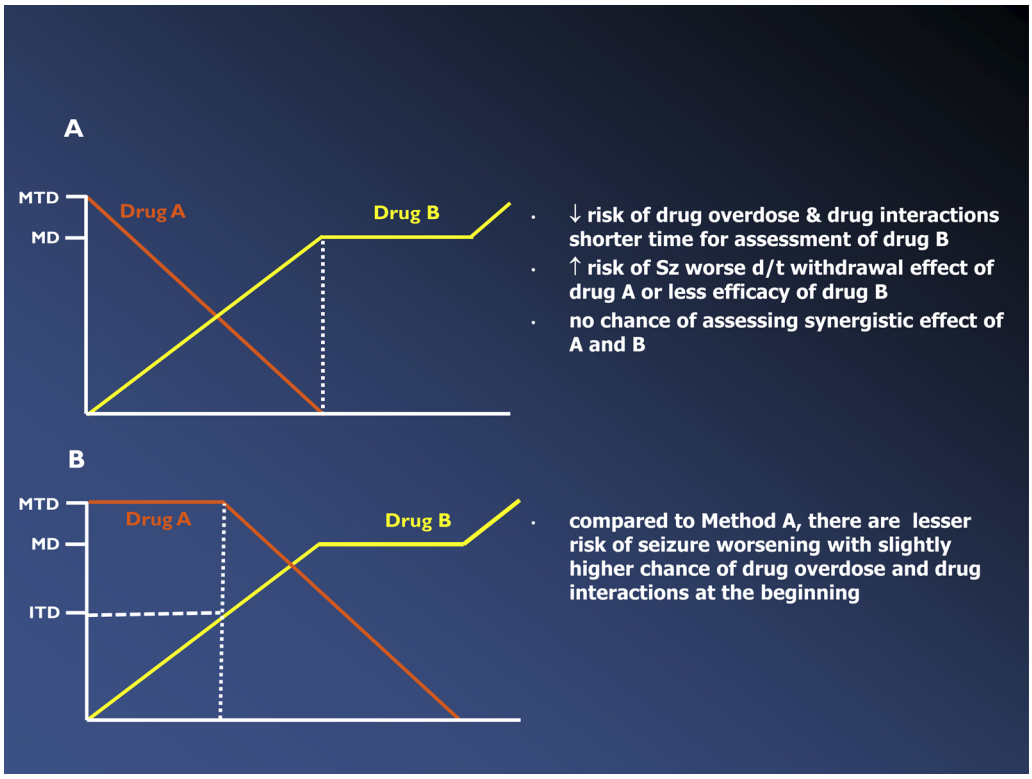

Fig. 3. Methods of Substitution Monotherapy.
A. Simultaneous introduction of drug B and withdrawal of drug A is performed to achieve substitution monotherapy of drug B during a shorter period. Once the dose of drug B reaches to the moderate dose, a period of careful assessment of drug responsiveness is required before further dose escalation up to the maximal tolerable dose. This method has advantages of avoiding drug overdose, drug interactions and faster assessment of efficacy of drug B. However, it may increase risk of seizure worsening related to the withdrawal effect of drug A or less efficacy of drug B. There is no chance to assess any synergistic interactions of drug A and B.
B. Drug A is maintained until drug B is reached to the initial target dose, when the tapering of drug A starts while the dose of drug B is further escalated up to moderate dose and then to maximally tolerable dose. Compared to method A, there is lesser risk of seizure worsening with slightly higher chance of drug overdose and drug interactons at the beginning of introduction of drug B. Others are same as method A.
MTD; maximally tolerable dose, MD; moderate dose, ITD; initial target dose.

but avoiding drugs having adverse pharmacological (pharmacokinetic and/or pharmacodynamic) interactions, similar side effects profiles, and narrow therapeutic index. In clinical practice, several combination regimens have been reported to carry synergistic interactions (Rowan et al., 1983; Deckers et al., 2000; Kinirons et al., 2006; Stephen et al., 1998; Chung et al., 2010; Brigo et al., 2013; Brodie, 2016; Legge et al., 2018) (Table 1). Synergistic interaction of lamotrigine (LTG) and VPA combination therapy was first reported by Brodie and Yuen (1997), who found a much higher responder rate in add-on therapy of LTG in patients under VPA monotherapy than patients taking either CBZ or PHT monotherapy. Pisani et al. (1999) conducted a small-scale, systematic sequential drug trial of LTG and VPA to find the combination being highly effective in patients who were resistant to the monotherapy of both VPA and LTG. Synergistic interactions of LTG and VPA combination was further supported by many clinical investigations (Kanner and Frey, 2000; McCabe et al., 2001; Moeller et al., 2009; Poolos et al., 2012; Lee et al., 2018). For other combination regimens, clinical evidence is still limited and mostly at the level of case series or clinical observation (Abou-Khalil, 2017). Objective assessment of their clinical usefulness by well-designed clinical investigations are in urgent need.

2.3. Controversies on monotherapy and polytherapy

In debates of "Monotherapy vs. Polytherapy", major advantages of monotherapy are claimed to include, (1) simple regimen providing better compliance and help identify patients' response to individual drug, (2) less side effects or seizure worsening from lack of adverse drug interaction, and (3) less costly (Deckers, 2002; St. Louis et al., 2009), whereas proponents for polytherapy insist, (1) synergistic effects of combination drug regimen may provide either better efficacy or less toxicities, (2) new AEDs are less toxic, thus their combinations in appropriate doses may be better tolerable, (3) cost of having more seizures are more expensive than medication costs, (4) if combination works, conversion to substitution monotherapy would be riskier (Deckers, 2002; St. Louis, 2009; Brodie and Sills, 2011; Barker-Haliski et al., 2014). All these comments are probably true but may work differently on case by case, thus physicians are required to be more flexible in adopting different mode of pharmacotherapy to the clinical practice for different clinical scenarios. Careful analysis of evidence about the current status of major issues in debates may help physicians take more flexible approaches in pharmacotherapy of real world practice.

2.3.1. Does Monotherapy carry better compliance than polytherapy?

Poor compliance (or drug non-adherence) is an important issue in epilepsy, which negatively affects patient outcomes including higher risks of accident, premature mortality, unemployment, hospital admissions or emergency room (ER) visits, and poor QOL (Faught et al., 2009; Shorvon, 2000). It has been a traditional concept that a simple drug regimen carries a better compliance, thus monotherapy was more favored than polytherapy. Drug-nonadherence rate in epilepsy is comparable to other chronic illnesses (e.g., hypertension, diabetes mellitus, etc.) being reported 25%–66% (O'Rourke and O'Brien, 2017). Factors related to drug-nonadherence in epilepsy are multiple, which can be categorized into patient-related, disease-related, medication-related, health-care related, and socio-economic factors. Among those, patient-related factors are probably most important because side-effects and long-term effects of AEDs are major concerns of patients toward AEDs (Chapman et al., 2014; O'Rourke and O'Brien, 2017). Chapman et al. (2014) reported that 47% of patients preferred to risk a seizure than take epilepsy medication with the nonadherence rate being directly related to the patient's concept on drug-necessity and drug-concerns scores. Among medication-related factors, dosing frequency was the single most important factor affecting the medication adherence. Compared with once-daily dosing, regimen adherence was 13.1%, 24.9%, and 23.1% lower in twice-, 3-times, and 4-times daily regimens (Coleman et al., 2012). On the other hand, studies have shown conflicting results for monotherapy vs. polyhtherapy. Guo et al. (2015)

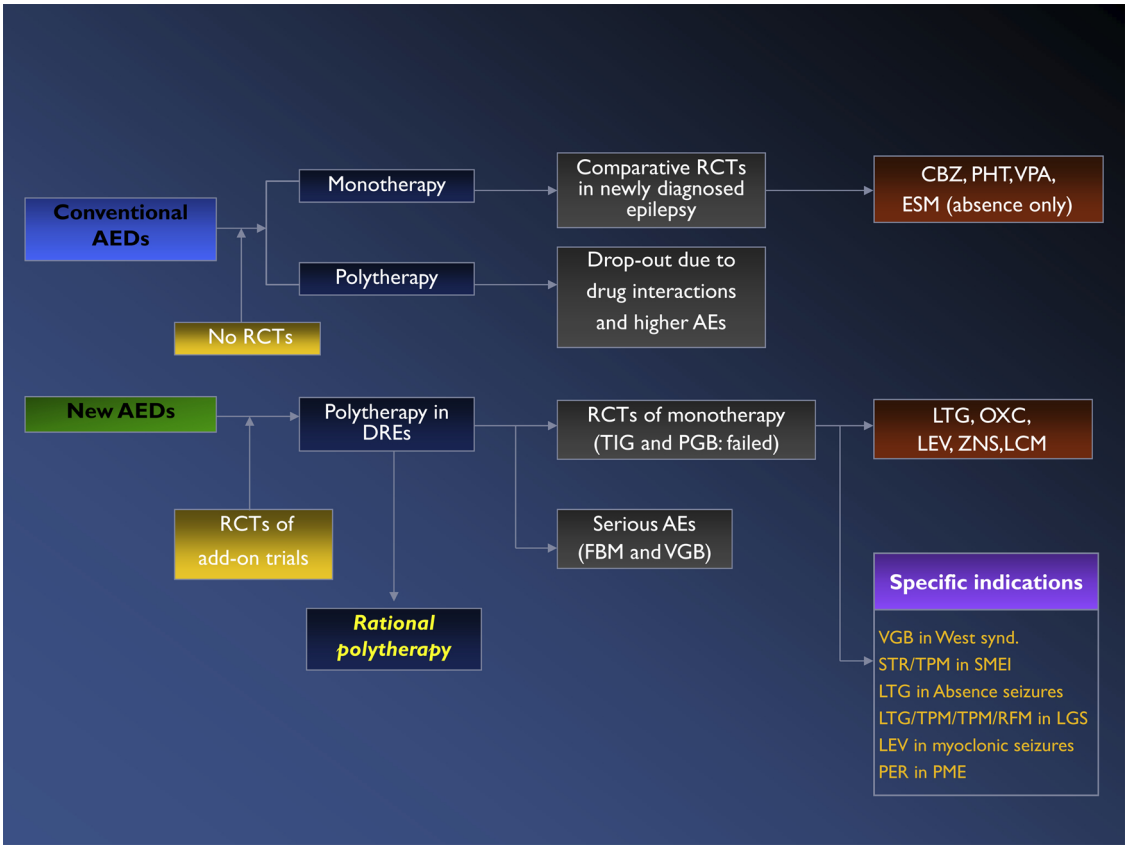

Fig. 4. Clinical Development of AEDs.
Conventional AEDs were introduced to the market without any RCTs and used in both monotherapy and polytherapy. After many years of clinical experiences, monotherapy RTCs in patients with newly diagnosed epilepsies were undertaken to promote CBZ, PHT, and VPA as first-line drugs for focal epilepsy, VPA for generalized seizures and ESM in absence epilepsy. New AEDs were introduced to the market after rigorous RCTs of add-on therapy in patients with drug resistant epilepsies (DREs) taking 1–3 AEDs to demonstrate superior efficacy of new AEDs to placebo. New AEDs obtained their marketing approval primarily for their use as add-on therapy for patients with DREs taking other AEDs, which has stimulated physicians to exercise various forms of polytherapy and to establish the concept of rational polytherapy. After many years of their use in polytherapy, they underwent monotherapy trials to be promoted as first-line drugs for focal seizures with or without bilateral tonic-clonic seizures. In addition, through phase 4 clinical trials, several new AEDs were found to have excellent efficacy in a few specific epilepsy syndromes.
CBZ; carbamazepine, ESM; ethosuximide, FBM; felbamate, GBP: gabapentine, LCM: lacosamide, LEV: levetiracetam, LTG; lamotrigine, OXC; oxcarbazepine, PGB; pregabalin, PRP; perampanel, RFM; rufinamide, STR: stiripentol, TIG; tiagabine, TPM; topiramate, VGB; vigabatrin, DREs; drug resistant epilepsies, LGS; Lennox-Gastaut syndrome, PME; progressive myoclonic epilepsy, SMEI; severe myoclonic epilepsy in infancy (Dravet syndrome).

Table 1
Combination regimens carrying synergistic interactions.

Combination Regimen	Level of Evidence	References
LTG and VPA	+ + +	Brodie and Yuen(1997); Pisani et al.(1999)
ESM and VPA	+ +	Rowan et al. (1983), in absence seizures
LTG and TPM	+	Stephen et al. (1998)
LCM and LEV	+ +	Chung et al. (2010)
LTG and LEV	+ +	Kinirons et al.(2006); Legge et al.(2018)
OXC and LEV	+	Legge et al.(2018)
CBZ and VPA	+	Stephen et al. (2012)
CBZ and TPM	+	Brodie (2016)
CBZ and LEV	+	Brodie (2016)
CBZ and GBP	+	Brodie (2016)
VPA and LEV	+	Brodie (2016)
VPA and CLB and STR	+ + +	Chiron et al. (2000), in Dravet syndrome
LTG and VPA and BDZ	+ +	Machado et al. (2011), in epileptic encephalopathy
VGB and Hormones	+ + +	O'Callaghan et al.(2017), in infantile spasm

+ + +; controlled trials, + +; case series studies, +; anecdotal.
BDZ; benzodiazepines, CBZ; carbamazepine, ESM; ethosuximide, CLB; clobazam, LCM; lacosamide.
LEV; levetiracetam, LTG; lamotrigine, OXC; oxcarbazepine, STR; stiripentol, VGB; vigabatrin, VPA; valproate.
Regimens containing phenobarbital was excluded due to lack of clinical benefit related to the poor tolerability of phenobarbital.

reported that the prevalence of moderate to high drug-adherence was 58% in monotherapy and 62% in polytherapy. In a population based study (Gollwitzer, et al., 2016), higher adherence to AEDs was related with new AED than old AED and branded drugs than generics but not to the mode of pharmacotherapy. Therefore, any differences between monotherapy and polytherapy in their impacts on drug-adherence are neither evidence-based nor relevant.

2.3.2. Is polytherapy associated with adverse drug interactions?

Drug interactions are relatively common during polytherapy and often implicated as being responsible for adverse therapeutic outcomes. Drug interactions in combination therapy include both pharmacokinetic and pharmacodynamic interactions (Patsalos, 2013; Perucca, 2006). Pharmacokinetic interactions of combination drug regimens are easily predicted and handled by appropriate dose adjustments on the basis of pharmacokinetic profiles of individual drugs, while it is expected not to change the therapeutic index of each drug. Pharmacokinetic interactions are usually precipitated by combining drugs which are either inducers or inhibitors of hepatic metabolizing enzymes (CYP 450 enzyme system and glucuronide conjugation enzyme system). Although plasma protein binding interactions may be relevant to highly protein-bound AEDs (PHT or VPA), their impact is short-lived and usually of little clinical significance (Perucca, 2006). Most conventional AEDs are metabolized in the liver and either broad hepatic enzyme inducers (CBZ, PHT, PB, and primidone) or inhibitors (VPA), thus combining conventional drugs are frequently associated with significant pharmacokinetic interactions, which are often clinically undesirable. Enzyme-inducing AEDs (EI-AEDs) usually increases the clearance of partner drugs to precipitate using higher doses, which may also increase the concentration of metabolites being potentially toxic (Wagner et al., 1993; Bernus et al., 1997). It may also shorten the half-life of AEDs to cause larger fluctuations of effective serum concentration, precipitating more frequent exposure to higher peak levels as well as lower trough levels, which may increase chances of either neurotoxicities or breakthrough seizures. In addition, EI-AEDs adversely affects endogenous metabolisms to cause risks of bone health, high cholesterol and vascular risk factors, as well as sexual dysfunction, thus EI-AEDs are not regarded as first-line drugs any longer (Mintzer and Mattson, 2009; Brodie et al., 2013). Therefore, major adverse pharmacokinetic interactions in AEDs therapy are not related to the polytherapy per se, but the inclusion of EI-AEDs in the regimen. In fact, many new AEDs are neither broad-spectrum enzyme inducers nor substrates of hepatic metabolism, thus the potential of adverse pharmacokinetic drug interactions of their combinations are significantly reduced or even can be completely avoided by careful consideration of pharmacokinetic profiles of individual drugs (St. Louis, 2009; Patsalos, 2013). Pharmacodynamic interactions are primarily related to MOAs of individual drug and directly affect the therapeutic index of each drug (Perucca, 2006), which are divided into additive, supra-additive, and infra-additive interactions in either therapeutic or adverse effects (Kwan and Brodie, 2006). Apparently, the rationale of polytherapy is to combine drugs carrying synergistic interactions (supra-additive efficacy or infra-additive toxicity) to improve therapeutic index of the regimen. However, clinical assessment of pharmacodynamic interactions of the regimen is difficult and we don't have any ideal trial designs for clinical testing of pharmacodynamic interactions yet. In animal experiments, they are measured by either isobolographic analysis or direct measurement of therapeutic index in specific animal models (Deckers et al., 2000; Luszczki and Czuczwar, 2004 Kaminski et al., 2009; Lason et al., 2011), which have disclosed that combining drugs having different MOAs are usually associated with synergistic interactions to support the principal concept of rational polytherapy. In clinical trials, combinations of drugs having sodium-channel blocking effects were found to have higher incidence of AEs and premature withdrawal from the study than combinations of a sodium-channel blocker and a drug having different MOAs (Besag et al., 1998; Barcs et al., 2000). Sake et al. (2010) reported that add-on of lacosamide (LCM, inhibitor of slow inactivation of sodium channels), to drugs having sodium channel blocking effect resulted in a lesser efficacy and higher AEs compared to the add-on of LCM to non-sodium channel blockers. Margolis et al. (2014), analyzed a large insurance database to find that various combinations of drugs having same MOA were associated with higher rates of discontinuation, higher risk of inpatient admission and emergency department visits compared with the combination of drugs having different MOAs, which was supportive for the hypothesis of MOA-driven synergistic interactions. In fact, combining drugs having different MOAs has been the general principle in medical treatment of chronic diseases (e.g., essential hypertension, diabetes mellitus, cancer, etc.) by virtue of availability of drugs having diverse MOAs. In pharmacotherapy of epilepsy, similar principle is being adopted as many different classes of new AEDs being available.

2.3.3. Is polytherapy associated with higher incidence of side effects?

Earlier clinical studies suggested that polytherapy was associated with higher prevalence of side effects and its conversion to monotherapy resulted not only improvement of seizure control but also side effects (Shorvon and Reynolds, 1979; Schmidt, 1982). In addition, a large number of hospital cohort studies often reported that polytherapy was associated with higher prevalence of side effects (Cramer et al., 2004; Carreno et al., 2008). However, Kwan and Brodie (2000b) reported that the incidence of intolerable AEs was numerically higher in substitution monotherapy than duotherapy (26% and 12%, respectively), although it failed to reach statistical significance probably due to a small sample size. In an open-randomized comparative trial of substitution monotherapy with duotherapy (Beghi et al., 2003), incidence of side effects was 51% in monotherapy and 34% in duotherapy, which has shown a trend for better tolerability of duotherapy ($P = 0.07$). Lammers et al. (1995) quantified TDL to correlate with the prevalence of side effects in 423 patients. Prevalence of AEs was similar between monotherapy and polytherapy when TDL ≤ 2, whereas none of patients under monotherapy but almost 60% of patients under polytherapy were taking TDL > 2. The study concluded that patients on polytherapy were able to tolerate higher TDL and the emergence of AEs in patients under polytherapy was not related to the number of drugs but a higher TDL in polytherapy than monotherapy. In an Italian multicenter study (Canevini et al., 2010), which was conducted in the era of new AEDs, there was no difference in side effects between patients under monotherapy and polytherapy, whereas TDL was ≤ 2 in a majority of patients under monotherapy but usually ≥ 2, often ≥ 4, in patients under polytherapy without reporting any side effects. Authors hypothesized that AEs are determined more by individual susceptibility, type of AEDs used, and physicians' skills than number of AEDs and TDL. Therefore, previous assumption of monotherapy being associated with less side effects than polytherapy is probably not tenable any more in the era of new AEDs.

2.3.4. Are monotherapy and polytherapy same in efficacy?

Schmidt (2002, 2003) investigated outcomes after "conversion to monotherapy" in patients under maximally tolerable duotherapy and after "add-on of second drug" in patients under monotherapy at MTD to report highly comparable outcomes between two regimens. Deckers et al. (2003) reviewed previous observational studies and found that mean seizure free rates (SFRs) were 25% (12%–45%) in four studies of substitution monotherapy and 23% (15%–35%) in five studies of duotherapy. In two representative studies comparing substitution monotherapy with duotherapy (Kwan and Brodie, 2000b; Beghi et al., 2003), SFR was numerically higher in duotherapy but failed to reach statistical significance. However, no double-blind RCTs comparing monotherapy with polytherapy in patients with DREs or who failed to initial monotherapy have been conducted yet, which is largely responsible for the persisting controversy. In fact, a fair comparison of monotherapy and combination therapy requires balanced baseline patient characteristics,

appropriate dose-titration schedules including initial target dose (ITD), equivalent TDL between two groups, as well as appropriate selection of combination regimens, preferably consisting of drugs carrying synergistic interactions (Deckers et al., 2001; Barker-Haliski et al., 2014; Lee et al., 2018). These requirements are difficult to meet in trials of patients who failed to previous AEDs therapy, but may be feasible in newly diagnosed patients. Deckers et al. (2001), conducted a study comparing CBZ monotherapy with combination therapy of CBZ and VPA as initial treatment regimen in patients with untreated epilepsy, which was the only double-blind RCT comparing monotherapy with combination therapy in equivalent TDL. Outcome measures were numerically in favor of combination therapy, but differences were not statistically significant. Criticisms against the study may include that the combination of CBZ and VPA has significant pharmacokinetic drug interactions (Bernus et al., 1997) and no proven synergistic interactions. Another important criticism against the study at the time of its publication was that we did not need a combination drug regimen as the first drug regimen, thus the study failed to implement any further comparative controlled trials of monotherapy and polytherapy in newly diagnosed patients. However, as polytherapy become more widely used and some combination regimens being considered to have synergistic interactions, a fair comparison of specific combination regimens with monotherapy was considered clinically meaningful. Lee et al. (2018) conducted an open randomized trial comparing the CBZ-CR monotherapy and lamotrigine (LTG) and VPA combination therapy in equivalent TDL in newly diagnosed or untreated patients with FS. Completion rate, the primary outcome measure, was not different between the groups. However, secondary efficacy measures which were SFR during 52 weeks of maintenance phase and time to first seizure during maintenance phase, were significantly in favor of combination therapy, which has suggested a higher efficacy of LTG and VPA combination to CBZ-CR monotherapy as the initial drug regimen. Kwan and Brodie (2000a), in a systematic drug trial of 470 patients with newly diagnosed epilepsy, reported that SFR was 47% in first drug monotherapy and 13% in second drug monotherapy, but, after failure of first two drugs, it was only 1% in third drug monotherapy compared to 3% of combination therapy. Therefore, combination therapy seems to contribute only a small fraction of seizure freedom, but it was three times higher than monotherapy in patients who failed to first two drug regimens. Reassessment of extended population from the same institution 10 years later showed that the overall outcome of patients with newly diagnosed epilepsy were not much different but more patients did well on polytherapy with the increase of seizure freedom by polytherapy from 3.0% to 6.4% (Brodie et al., 2012), more than 2-fold increase. More recent analysis of the same hospital cohort (Chen et al., 2018) reported a similar finding, no improvement of seizure freedom by monotherapy but further increase of seizure freedom by combination therapy, which was 8.4%. The 30-year longitudinal hospital cohort observation study has clearly indicated that polytherapy was associated with a progressive increase of SFR by almost three fold, whereas seizure freedom by monotherapy being stagnant around 60%. These studies may suggest that clinical impacts of new AEDs are more pronounced in polytherapy than monotherapy.

3. Employment of polytherapy in sequential pharmacotherapy

Modern pharmacotherapy of epilepsy consists of an orderly administration of drug trials in a sequence of first, second, third, and next drug regimens (Mohanraj and Brodie, 2006; Brodie et al., 2012). First drug monotherapy is the standard mode of therapy as the first step of sequential drug trials. However, if the first drug failed to control seizures, expert opinions for their preferred mode of therapy as the next step of drug trial have been far from reaching to a consensus (French and Faught, 2009). Reassessment of previous concept of polytherapy related to monotherapy, which was established during the era of conventional AEDs, may raise a question, “when should we employ polyhtherapy in the algorhithm of sequential drug trials?”, an important issue in real world practice.

3.1. After failure of adequate trials of two first-line drugs

During the era of conventional AEDs, definition of DRE was not unified and most experts considered that failure of at least three drugs in monotherapy were necessary to satisfy the definition of DREs (Bourgeois, 2000a,b). Therefore, polytherapy was attempted at later stages in the sequential pharmacotherapy, usually after exhaustive trials of substitution monotherapies. However, since ILAE proposed the definition of DREs as epilepsy unresponsive to adequate trials of two drug regimens (Kwan et al., 2010), employment of polytherapy including new drugs in the regimen has been attempted one step earlier than before. French and Faught (2009) suggested that polytherapy is preferred after the failure of appropriate monotherapy trials of first two AEDs. Although a majority of US-experts are still in favor of third drug substitution monotherapy after failure of first two drug monotherapies (Shih et al., 2017), consensus from European experts are in favor of combination therapy (Semah et al., 2004; Legros et al., 2009). Luciano and Shorvon (2007) reported that successive introduction of new AEDs in add-on therapy of patients with chronic refractory epilepsy resulted prolonged seizure freedom in 28% of patients. Choi et al. (2016) reported that further drug trials in 403 patients who failed to first two drugs due to insufficient efficacy resulted in prolonged seizure remission in 31%. Therefore, in real world practice, serial drug trials were successful in about a third of patients with DREs, which is a significantly better outcome than our previous expectation (Schmidt, 2002) and a strong message to caring physicians for the importance of continuing optimized drug trials even after the diagnosis of DREs. In an Italian multicenter study (Canevini et al., 2010), only 25% of 191 children and 21% of 933 adults with DREs were under monotherapy, thus a majority of patients with DREs were on polytherapy. Data from real world practice indicate that polytherapy is the major mode of pharmacotherapy in patients satisfying the ILAE criteria of DREs, which justify the placement of polytherapy in the next step after the trial of second drug therapy (French and Faught, 2009; Stephen and Brodie, 2012).

3.2. After failure of first drug

If the first drug monotherapy failed to control seizure at MTD, the next step is the adequate trial of second drug. However, the optimal mode of therapy for second drug trial is probably the most controversial step in the algorhithm of sequential drug trials. In addition to previously cited studies, which have failed to show any significant differences between substitution monotherapy and polytherapy (Deckers et al., 2003; Kwan and Brodie, 2000b; Beghi et al., 2003), a French open comparative trial (Semah et al., 2014) of substitution monotherapy and add-on therapy of second drug in patients who failed to the first monotherapy did not reveal any significant differences in efficacy, tolerability, and QOL measures. An Italian multicenter observation study (Millul et al., 2013) also found same outcomes in retention rate, QOL measures, hospital admissions and days off-work and off-school between substitution monotherapy and add-on therapy of second drug but a slightly higher incidence of AEs in patients underwent substitution monotherapy. Therefore, comparative studies of substitution monotherapy and add-on therapy of second drug in patients who failed to first drug monotherapy universally failed to detect any significant differences between two modes of therapy. However, none of these studies compared any specific combination regimens to substitution monotherapy. As found in the subgroup analysis of a single center study (Kwan and Brodie, 2000b), in which a specific combination regimen consisting of a sodium channel blocker and a drug having multiple MOAs was significantly superior to other combination regimens, future trials need to consider the comparison of specific combination regimens

carrying synergistic interactions with substitution monotherapy regimens.

French and Faught (2009) recommended substitution monotherapy as the primary mode of therapy in patients who failed to first drug monotherapy, however, they also suggested to consider combination therapy in following clinical scenarios; (1) if first drug was at least partially effective, (2) if no drug interactions are anticipated by second drug add-on, (3) if patients are risk-averse or risk of seizure exacerbation is high at the withdrawal of first drug, and (4) if patients tolerate first AED well. These recommendations clearly suggested that the conduct of substitution monotherapy is not a dogma anymore but caring physicians need to choose the appropriate mode of therapy on a careful assessment of causes of first drug failure, pharmacological profiles of first and second drugs, and patient's clinical profiles. One way of avoiding these theoretical arguments is to adopt "transitional polytherapy" (Deckers et al., 2003; Garnett et al., 2009) in the process of second drug administration. Once the second drug was chosen, the next step is to introduce a small dose followed by slow dose escalation of the second drug up to ITD, when duotherapy of first and second drugs is continued at least for 3 months (or longer than three times of longest interseizure interval) to monitor seizure control and tolerability. If seizures were fully controlled without any adverse reactions, duotherapy is continued for extended period of time, at least for 1 year or longer, when the feasibility of substitution monotherapy of second drug may be discussed with the patient for further long-term treatment. If seizure control was excellent but associated with side effects, reduction of the dose of first drug is attempted to decrease TDL (Naritoku et al., 2005). If duotherapy was associated with significant improvement but not a complete seizure control, dose of second drug will be increased slowly with simultaneous slow tapering of first drug until complete seizure control is achieved or patient develops side effects, when substitution monotherapy of second drug is maintained for the assessment of its clinical outcome. Because patients under polytherapy are liable to the exposure of excessive drug burden, a careful assessment of tolerability should be repeated at every clinical visit during the period of transitional polytherapy, preferably using an instrument like Liverpool Adverse Effects Profiles (LAEP) (Baker et al., 1994; Perucca et al., 2000). If first duotherapy did not improve seizure control, second drug is withdrawn along with the introduction of third drug in a similar fashion. Transitional polytherapy may take a longer time than substitution monotherapy for outcome assessment but have advantages of low risk of seizure worsening from the withdrawal of first drug and assessment of potential synergistic interactions of combination drug regimen (Fig. 5), which may provide a flexibility to caring physicians in choosing the optimal mode of therapy for given individual clinical scenarios.

3.3. Polytherapy as the initial drug regimen

Monotherapy is the gold standard of the first drug trial in the algorithm of sequential drug trials, thus employment of polytherapy as the initial step of pharmacotherapy is unlikely to be considered unless any compelling reasons are provided. Traditional concept of monotherapy is based on the assumption that a single drug trial of appropriate dose provides better effectiveness than polytherapy, thus first drug is started at a low dose to be slowly increased up to ITD. If seizures continued at ITD of first drug, doses are further escalated to find the optimal dose, until the patient becomes seizure free or develops intolerable adverse effects. Therefore, the trial of monotherapy of MTD is considered essential before the failure of monotherapy is declared. Although the concept of monotherapy of MTD has gained a wide acceptance, it has become widely recognized that seizure freedom by monotherapy is largely achieved at low to moderate doses. Deckers et al. (2003) from the analysis of dose related seizure freedom in previous RCTs of monotherapy in newly diagnosed epilepsy, reported that SFR of monotherapy was 11.9% at low dose, which was increased by 37.2% at its dose-escalation to average dose, by 7.7% at high dose, and further by 5.2% at MTD, whereas all patients exposed to MTD had dose-related side effects. Kwan and Brodie (2001) showed that more than 90% of seizure-free patients were taking moderate doses or less of different AEDs; e.g., CBZ 800 mg/day, LTG 300 mg/day, and VPA 1500 mg/day. The RCT of CBZ-CR and LEV monotherapy in newly diagnosed epilepsy (Brodie et al., 2007) revealed that SFR in LEV monotherapy group were 48.7%, 54.4%, and 56.6% at 1000 mg/day, 2000 mg/day, and 3000 mg/day, respectively, which were 52.2%, 58%, and 58.5% at CBZ-CR 400 mg/day, 800 mg/day, and 1200 mg/day, respectively. Rhee et al. (2017) reported that more than 90% of patients under monotherapy or combination therapy of LEV with seizure freedom were taking 2000 mg/day or less. Therefore, the likelihood of achieving seizure freedom by escalating the dose of first drug beyond the moderate dose is low, less than 10%, whereas the risk of dose-related AEs is high. Although careful monitoring of side effects and judicious handling of dose escalation may help avoid emergence of AEs, the concept of monotherapy of MTD implies that, if seizures were not controlled by moderate dose, most patients are going to experience dose-related toxicities during the process of further dose adjustment. Caring physicians should explain and encourage patient to freely communicate with him for early detection of AEs and should know that patients' spontaneous reporting of side effects is less reliable compared to the use of formal AEP-scoring questionnaires (Carreno et al., 2008). A small but definite risk of seizure worsening by high dose or MTD monotherapy is another concern, which is often called paradoxical seizure worsening (Perucca et al., 1998). This phenomenon was mostly reported in cases taking high dose PHT but it may also occur in other AEDs trials (Osorio et al., 1989). Recently, Poolos et al. (2017) compared seizure frequencies related to each quartiles of drug doses among monotherapies of CBZ, PHT, VPA, LTG, and combination therapy of LTG and VPA in patients with chronic refractory epilepsies and mental handicaps. The seizure control was better in patients exposed to the lowest dose quartile of all four monotherapies with showing negative dose-response relationship in higher quartiles of dose. On the other hand, responses to LTG and VPA combination therapy showed a positive relationship in all four dose ranges of LTG. This study has provided an example of striking difference in dose-response relationship between monotherapy and polytherapy. However, the study population was different in clinical characteristics from patients with newly diagnosed epilepsy and relatively high doses were administered, thus a caution is required in applying this phenomenon to general neurology clinics.

In the era of new AEDs carrying more than 25 AEDs to use, our adherence to the monotherapy of MTD may not be necessarily advantageous to some patients who are willing to achieve earlier seizure control with less risk of side effects. In those patients, if a moderate dose of first drug failed to control seizures, adoption of second drug therapy in the form of transitional polytherapy seems a viable option to consider than continuing dose-escalation up to MTD (Deckers et al., 2003; Rhee et al., 2017). Although we don't have any controlled trials comparing outcomes of the first drug monotherapy of MTD with the combination therapy of first and second drugs in patients who were not responsive to a moderate dose of first drug monotherapy, a recent hospital observation study (Chi et al., 2018) showed a significantly different outcome favoring combination therapy than monotherapy of MTD, which should be an important target for future research. If we could adopt a reliable model predicting future seizure outcome at each clinic visit, it may make sense to try combination therapy in patients having a low chance of seizure remission by monotherapy of MTD before they develop dose-related AEs (Hughes et al., 2018).

The current concept of pharmacotherapy implies that add-on of second drug is considered only when adequate dose of first drug failed to control seizures. Therefore, adoption of polytherapy as the initial drug regimen is not easily applicable but should require the fulfillment of following conditions, (1) availability of class 1 evidence in favor of polytherapy than monotherapy as the initial drug regimen, (2)

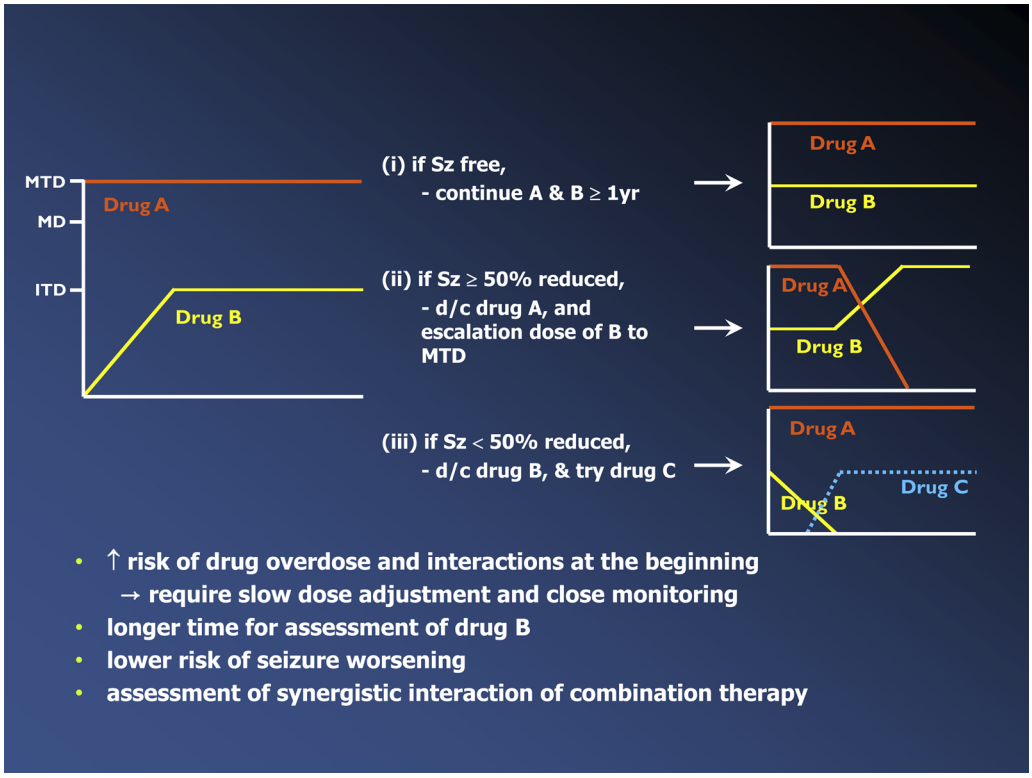

Fig. 5. Method of Transitional Polytherapy.
Drug A is maintained until drug B is reached to ITD, when the combination of drug A and drug B is maintained for a certain period, usually about 3 months (or at least for three times of longest interseizure intervals), to assess the effects of combination therapy. (1) If a patient become seizure free, their combination is maintained for long-term use, usually for 1 year or longer, when a possible substitution monotherapy will be discussed with the patient. (2) If there was a significant improvement of seizure control but not completely seizure free, dose of drug B is gradually increased with simultaneous withdrawal of drug A to achieve maximally tolerable dose substitution monotherapy of drug B. If seizures get worse, either drug A is reintroduced or drug C is going to be introduced in similar fashion. (3) If there was no significant improvement of seizure control after introduction of drug B, drug C is chosen to be introduced while drug B is tapered off to assess the responses to the combination of drug A and drug C. Transitional polytherapy has disadvantages of drug overdose and drug interactions during the period of introduction of drug B and its maintenance at ITD, which requires slow dose escalation and close monitoring of adverse effects. It may also take much longer time for the assessment of efficacy of drug B either in combination therapy with drug A or later monotherapy. However, it carries advantages of lower risk of seizure worsening and assessment of synergistic interactions of combination therapy.
MTD; maximally tolerable dose, MD; moderate dose, ITD; initial target dose.

identification of specific epilepsy syndromes or patient groups having a high risk of intractability to monotherapy, e.g., West syndrome, Lennox-Gastaut syndromes or other severe epilepsy syndromes, etc., and (3) presence of reliable evidence supporting for the benefit of earlier seizure control related to the favorable long-term consequences. In fact, a large-scale open-label RCT compared the combination of hormonal therapy and VGB with the hormonal therapy alone in children with newly diagnosed infantile spasm (O'Callaghan et al., 2017) has provided a high quality evidence for the superiority of combination therapy to monotherapy in this highly refractory childhood epilepsy syndrome. The comparative trial of LTG and VPA combination and CBZ-CR monotherapy in newly diagnosed focal onset seizures also favored the combination regimen in terms of higher SFR and longer time to seizure recurrence (Lee et al., 2018). These pieces of evidence for advantages of polytherapy as the initial drug regimen in diverse clinical scenarios (O'Callaghan et al., 2017; Lee et al., 2018; Chi et al., 2018) need to be translated into large- scale, comparative trials of monotherapy with specific combination regimens.

As Brodie et al. (2012) reported that 72.7% of the seizure free patients did so on first drug monotherapy, the major impact of first drug-regimen on the overall outcome of pharmacotherapy has been widely recognized (Schiller and Najjar, 2008) to stress the importance of maximizing the outcome of first drug regimen for further improvement in the overall outcome of pharmacotherapy. However, if we consider that all previous comparative monotherapy trials of new AEDs in patients with newly diagnosed focal epilepsy failed to demonstrate any differences in efficacy from conventional AEDs (Kwan and Brodie, 2003; Tudur Smith et al., 2007; Lattanzi et al., 2019), the strategy of sticking to the monotherapy as the first drug regimen is unlikely to improve the outcome of pharmacotherapy further. As the longitudinal study of Glasgow hospital cohort over past three decades (Chen et al., 2018) clearly showed that the improvement of seizure free outcome was achieved only in patients treated by polytherapy, employment of polytherapy carrying synergistic interactions as the first drug regimen in patients with higher risks of DREs seems to be an attractive strategy requiring future controlled trials.

4. Polytherapy in real world practice

Comparison of monotherapy with polytherapy at each steps of sequential pharmacotherapy is based on the assumption that each mode of therapy consists of the best drug regimen for given clinical scenarios. Among conventional AEDs, CBZ was promoted as the best drug for FS, whereas VPA is for GS through many RCTs (Mattson et al., 1985; Mattson et al., 1992; Heller et al., 1995; de Silva et al., 1996). With a few exception of head to head monotherapy trials comparing new AEDs in patients with newly diagnosed epilepsy (Brodie et al., 2002; Kwan et al., 2011; Marson et al., 2007a, 2007b), new AEDs underwent comparative RCTs of initial monotherapy against conventional drugs, mostly CBZ in focal epilepsy, with quite comparable outcomes in efficacy and tolerability (Tudur Smith et al., 2007), which has determined the non-inferiority trial as a standard design of comparative monotherapy trials of new AEDs in Europe. On the contrary, none of specific combination drug regimens have been subjected to any comparative RCTs yet and diverse combination regimens were gathered into the polytherapy to compare with the monotherapy in diverse patient populations, which seems problematic to accept in current view. Considering polytherapy regimens are subjected to diverse pharmacodynamic interactions ranging from infra-additive to supra-additive interactions, future comparative clinical trials of monotherapy and polytherapy should select specific polytherapy regimens carrying synergistic interactions for a fair comparison.

No practice guidelines of polytherapy are available yet but a few expert's comments (Deckers, 2002; St. Louis, 2009; Brodie, 2016)

Table 2
Selection of AEDs for combination therapy.

Step 1. Candidate drugs for given clinical scenario[a]	Step 2. Selecting a drug best matching to first drug in combination
Drugs without previous exposure	Drug having different MOA
Drugs found effective at least partially in previous exposure in monotherapy	Drug having less or no pharmacokinetic interactions
Drugs having desirable MOAs	Drugs having different side effects profiles
Drugs not enzyme inducers	Drugs fitting to one of known combination regimens carrying synergistic interactions[b]
Drugs having positive effects on comorbidities	
Drugs having higher efficacy, safer, and better tolerability from EBM data	

[a] First-line drugs for the seizure types or epilepsy syndromes are preferred candidate drugs for the trial of first duotherapy, whereas they are extended to include second line drugs in subsequent polytherapy.
[b] Combination regimens enlisted in Table 1.

adopting the general concept of "Rational Polytherapy", which is still at the level of hypothesis than guideline. Therefore, individual experts may apply the concept in slightly different ways based upon their own experiences and knowledge to prescribe different regimens for a given clinical scenario (Shih et al., 2017). Despite lack of evidence, it seems making sense to synthesize the prescription in two steps (Table 2). First step is to list potential drugs considered useful to try in the given clinical scenario, which was suggested by Brodie (2016). For duotherapy, first-line drugs for the patient's seizure types and epilepsy syndrome are considered appropriate candidate drugs to add-on, if they were not exposed previously or, if previously exposed, they were effective at least partially in monotherapy and not associated with any serious AEs. These candidate drugs are going to be categorized by (1) MOAs, (2) pharmacokinetic profiles (enzyme inducer or inhibitor, or inducible), (3) drugs related to the patients' comorbidities (helpful, risky, neutral), and (4) efficacy, safety and tolerability data from EBM. Apparently adoption of these conditions for finding candidate drugs requires a thorough analysis of clinical profiles of given clinical scenarios. Second step is to choose the drug from the list, which is best matching to the first drug according to the principle of rational polytherapy, (1) drug having different MOAs from the first drug, (2) no or less pharmacokinetic interactions, (3) different side effects profiles, and (4) one of recognized combination regimens carrying synergistic interactions, which is enlisted in Table 1. For example, if the patient has focal seizures of unknown etiology and on CBZ-CR monotherapy without any exposure to other AEDs (Case Scenario 1), first-line drugs for focal epilepsy many include VPA, PHT, oxcarbazepine (OXC), LEV, LTG, ZNS, and LCM, among which OXC may be deleted from the list due to its similar pharmacological profile to CBZ-CR. LCM has not been officially promoted as the first- line drug yet, however, it was recently found to be non-inferior to CBZ-CR in a class-1 RCT of monotherapy in patients with newly diagnosed focal epilepsy (Baulac et al., 2017). Although topiramate (TPM) and GBP were proposed as first-line drugs by AAN/AES practice guidelines in 2004 (French et al., 2004a), they were withdrawn from the list in the recent practice guidelines (Kanner et al., 2018). These candidate first-line drugs are categorized according to their MOAs, pharmacokinetic profiles, patient's comorbidities, and their safety and tolerability. If the patient has depression, VPA, PHT, OXC, LTG are preferred, whereas LEV and ZNS are not. The next step is to choose the drug from the list best matching to CBZ-CR in the concept of rational polytherapy. As shown in the given case scenario, CBZ-CR and LEV combination seems to be the best matching combination regimen, which was recognized as having synergistic interactions in Table 1. A major concern of this combination regimen is the adverse psychiatric effects of LEV, which may aggravate preexisting depression or cause psycho-behavioral symptoms. Thus, accurate follow- up assessment as well as treatment of depression and/or other psychiatric symptoms after prescription of LEV are crucial for the success of the combination regimen. Considering that CBZ-CR is a broad-spectrum enzyme inducer, its switch to the monotherapy of less or non-enzyme inducing sodium channel blockers (e.g., OXC or LTG or LCM) may be a viable option before proceeding to the first duotherapy, thus subsequent combination regimens being better applicable to the principle of rational polytherapy.

Once the second drug was chosen for combination therapy, the next step is to conduct the second drug trial according to the principle of transitional polytherapy (Fig. 5). Because patients under polytherapy are liable to the exposure of excessive drug burden, a careful assessment of tolerability issues should be repeated at every clinic visit. At present, there is no consensus about how many drugs can be combined for polytherapy or when should we move to the triple drug combination therapy from duotherapy. Considering that there are many drugs having different MOAs, it seems worthwhile to try them on the basis of careful assessments of duotherapy. If first duotherapy was not effective, it seems better to switch less effective drug with third drug for the trial of second duotherapy. If the second duotherapy failed or if first duotherapy was effective but failed to achieve complete seizure freedom, it seems prudent to undertake first triple combination therapy by adding the drug of best preference. In fact, excellent outcome of triple drug combination therapy has been reported in patients suffering from severe epileptic encephalopathies (Chiron et al., 2000; Machado et al., 2011). Clinical trials of add-on therapy of new AEDs have shown that SFR was higher in patients with less baseline seizure burden than patients with higher seizure burden before the commencement of study drug (Heo et al., 2007; Cho et al., 2009), thus, if duotherapy reduced the patient's seizure burden significantly, trials of triple combination therapy may have better chance of seizure freedom, which may well be applied to the real world practice. However, if the duotherapy was not much effective, trials of alternative duotherapy by switching a drug with another drug chosen is preferred to find the best duotherapy regimen before moving into the trials of triple drug therapy. For those patients who failed to first doutherapy, the list of candidate drugs for subsequent combination therapy may be expanded to include non-first line drugs, e.g., GBP, PGB, TPM, clobazam, etc.

Pharmacotherapy in real world practice is not restricted to the reduction of seizure burden but should include improvement of QOL of the patients by optimizing broad aspects of patients' health, which includes control of comorbidities, psychosocial support, and control of drug-related AEs (Dalic and Cook, 2016; Shih et al., 2017). Prevalence of comorbidities in patients with epilepsy is 2–8 times of general population and about 50% of patients with epilepsy have at least one comorbidity, which is even higher in patients with DREs (Keezer et al., 2016). As we have many AEDs affecting non-epileptic conditions (Spina and Perugi, 2004; Stephen and Brodie, 2012), the choice of AEDs is not only directed to seizure types and epilepsy syndromes, but also to various comorbidities carried by patients. Comorbidities provide another concern for the risk of potential drug interactions between concomitant drugs and AEDs, which should be considered for the choice of AEDs. Among diverse comorbidities associated with epilepsy, depression and anxiety are the most common in patients with DREs, being present in 30%–60% and responsible for their poor QOL, but frequently under-recognized and under-treated (Fiest et al., 2013; Boylan et al., 2004; Kanner, 2017). These affective symptoms may have bidirectional relationship with epilepsy to interact each other affecting the clinical

Table 3
Choice of AEDs related to comorbidities in epilepsy.

Comorbidities	Choose	Avoid
Obesity ± DM	TPM, ZNS	GBP, PGB, VPA, PRP
Migraine	TPM, GBP, PGB, ZNS, VPA	
Skin rashes	LEV, GBP, PGB, TPM, VPA, PER, LCM	CBZ, LTG, OXC, PHT, PB
Neuropathic pain	PGB, GBP, CBZ, OXC, PHT, LTG	
Depression ± behavioral dis	LTG, CBZ, OXC, VPA, PGB	LEV, PB, TPM, ZNS, PER
Cognitive dysfunction	LTG, LEV, OXC, LCM	PB, TPM, ZNS
Concomitant drugs	GBP, LEV, PGB, LCM, ZNS	Enzyme- inducers or inhibitors
Cancer	LEV, VPA, PER	Enzyme- inducers
Cardiac arrhythmia		Sodium channel blockers
Glaucoma		TPM
Gait disturbances		CBZ. PHT, PER
Heat stroke		TPM, ZNS
Hematological disorder		CBZ, VPA
Hyponatremia		OXC, ESL, CBZ
Hepatic disease	Drugs excreted by renal excretion	VPA
Renal disease	Drugs excreted by hepatic metabolism	GBP, PGB, LEV
Hyponatremia		OXC, ESL, CBZ
Osteoporosis	LTG, LEV	Enzyme inducers, TPM, VPA, ZNS
Restless leg syndrome	GBP, PGB, CZP, PER	
Parkinson dis	ZNS	
Tremor	TPM, PB, PRM	

CBZ; carbamazepine, CZP; clonazepam, GBP: gabapentine, LCM; lacosamide LEV: levetiracetam, LTG; lamotrigine, OXC; oxcarbazepine, PB; phenobarbital, PRM; primidone, PER: perampanel, PGB; pregabalin, TPM; topiramate, VGB; vigabatrin, VPA; valproic acid, ZNS; zonisamide.

courses of epilepsy (Kanner, 2017). Although no convincing evidence is available yet for the use of second generation anti-depressants being being responsible for the improvement of seizure control, their use to manage affective disorders is an essential part of management to improve QOL and prevent suicidality. Depression is also responsible for higher prevalence of diverse AEs of AEDs therapy (Canevini et al., 2010; Kanner, 2017; Kim et al., 2015), which may be responsible for poor tolerability of AEDs and impaired adherence to AEDs therapy. Treatment of comorbidities in patients with epilepsy should be at a high priority to prevent suicide, improve QOL, and improve outcome of AEDs therapy. At present, we have a long list of drugs either to prefer or avoid in relation to various comorbidities (Table 3).

In conclusion, pharmacotherapy of epilepsy has become more diversified and sophisticated by introduction of many new AEDs having diverse MOAs, better pharmacokinetic profiles, and better tolerability profiles, which were instrumental for the concept of patient-oriented pharmacotherapy. Introduction of new AEDs also triggered a revival of polytherapy under the concept of Rational Polytherapy, which has become the mainstay of pharmacotherapy for patients with DRE, in whom a prolonged seizure freedom is achieved in about 30% of patients by systematic add-on drug trials. Previous criticisms against polytherapy including higher incidence of side effects, poorer QOL, or poorer adherence to AEDs are not supported any more in current view. It is likely that a significant improvement in the outcome of current AEDs therapy is feasible by earlier employment of polytherapy as well as identification of combination drug regimens carrying synergistic interactions. At present, LTG and VPA combination regimen is the only well documented synergistic regimen, but there are a long-list of candidate regimens requiring future trials in appropriate designs. As monotherapy and polytherapy have their own advantages and disadvantages, physician's attitude for a strict adherence to any specific mode of therapy seems to be out of date. We may need more flexibility in adopting a different mode of pharmacotherapy at each steps of sequential pharmacotherapy according to clinical profiles of individual patient in real world practice.

5. Case scenario

35 year-old male with focal epilepsy of unknown etiology having depression, who have failed to control seizures to initial monotherapy of CBZ-CR.

How to select second AED?

Step 1: First- line Drugs for Focal Seizures: PHT, VPA, LTG, LTG, LEV, ZNS, LCM, (OXC)

Categorize them into MOA, enzyme inducers or not, impact on comorbidities, and tolerability data from EBM

Step 2: Potential interactions with CBZ-CR related to the guideline of Rational Polytherapy

Step 1.	MOA	Enzyme induction	Comorbidity (depression)	Safety & tolerability
PHT	SCB	Inducer (-1)	Neutral (0)	Poor (-1)
VPA	Multiple	Inhibitor (0)	Help (+1)	Fair (0)
LEV	SV2A	None (0)	Risk (-1)	Good (+1)
LTG	SCB +	Inducible (0)	Help (+1)	Good (+1)
ZNS	Multiple	Inducible (0)	Risk (-1)	Fair (0)
LCM	SCB +	None (0)	Neutral (0)	Good (+1)

Step 2.	MOA	interactions	Side effects	Synergy	Total(step 1+2)
PHT	Overlap (-1)	High (-1)	Additive (-1)	No (-1)	−6
VPA	Different (+1)	High (-1)	Different (+1)	Yes (+1)	3
LEV	Different (+1)	None (+1)	Different (+1)	Yes (+1)	4
LTG	Partly- overlap (0)	Moderate (0)	Semi- additive (0)	No (-1)	1
ZNS	Different (+1)	Moderate (0)	Different (+1)	No (-1)	0
LCM	Partly- overlap (0)	None (+1)	Semi- additive (0)	No (-1)	1

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