Rational polytherapy: Myth or reality?

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SUMMARY

Background. The concept of rational polytherapy implies using a combination of antiepileptic drugs with synergistic effect, which in turn, may result in additive or reduced toxicity. This concept is not consensually accepted.

Aim. To present evidence in favour and against rational polytherapy.

Methods. Narrative literature review on PubMed and Medline databases using the following terms: epilepsy treatment, rational therapy/polytherapy, supraadditive treatment, drug-resistant epilepsy treatment. Cited references within selected articles were also evaluated.

Results. Against rational therapy is the evidence of clinical efficacy of the use of antiepileptic drugs with the same mechanism of action and without increased side-effects. Rational therapy may fail because while the addition of one antiepileptic drug to others with the same or different mechanisms of action leads to additive therapeutic efficacy, it also leads to more side effects. The evidence for the robust, unique, true synergism found between valproate and lamotrigine is questionable because the two drugs together may lead to complex pharmacokinetic interactions jeopardizing a consistent interpretation of the data. Data from studies with antiepileptic drugs with multiple mechanisms of action may be questionable because the same mechanism of action might not be responsible for drug efficacy or toxicity in different patients. Favouring rational therapy is the evidence that genetic animal models of seizures and drug-related neurotoxicity are ideal to evaluate the efficacy and toxicity of drug combinations, and that the most successful experimental combination of two antiepileptic drugs would be the one with a single mechanism of action and the other with a multiple mechanism of action.

Conclusion. Rational therapy is a sub-optimal, but worth being attempted strategy for the use of antiepileptic drugs in combination.

Key words: antiepileptic drugs • clinical efficacy • epilepsy • mechanisms of action • tolerability • therapy

BACKGROUND

Until the seventies and eighties of the last century, the pharmacological treatment of epilepsy was based on polytherapy and commercially available medications generally combining a barbiturate, phenobarbital (PB), with phenytoin (PHT). Then, the strategy changed and the regimen of monotherapy was established for the

treatment of epilepsy (Reynolds et al., 1976; Reynolds and Shorvon, 1981). During this period, whenever polytherapy was required, the rationale for choosing two antiepileptic drugs (AEDs) was based on the avoidance of combined pharmacodynamic or pharmacokinetic side effects (French and Faught, 2009).

In the ninth decade of the twentieth century, the so-called second-generation antiepileptic drugs (SGAEDs) started being commercialized. They had the advantages of better pharmacokinetic and pharmacodynamic profiles, less side effects and fewer drug interactions when compared with their first generation counterparts. Furthermore, several of them had novel mechanisms of action (MoA).

These properties of the SGAEDs lead to a re-evaluation of the polytherapy strategy and to new methods of choosing a second (or more) AED. This new approach was called rational polytherapy (RP) (Ferrendelli, 1995; Anonimous, 1995). In essence, RP consists of selecting combinations of AEDs that result in a greater clinical efficacy (additive or synergistic effect) compared to the one obtained by chance, but with additive or even infraadditive, toxicity. In other words, RP was defined as the association of different AEDs with unrelated MoAs, without complex pharmacokinetics interactions, with separate adverse events, and combined in moderate doses to produce major/synergistic effect (Mawer and Pleuvry, 1995). This novel idea of using AEDs with unrelated MoA arose from the growing body of evidence that combination of AEDs with different MoA would be an effective strategy to treat refractory epilepsies (RE) (Brodie and Sills, 2011).

The synergistic effect mentioned above has been well described (Mawer and Pleuvry, 1995). In short, whenever a similar dose of two AEDs is used the same effect will be obtained. If, however, a similar clinical effect is reached using a lower dose of one or both of the AEDs it is referred to as a synergistic effect. This is accomplished by using AEDs with fewer side effects and drug interactions and, preferentially, with different MoAs (Barker-Haliski et al., 2014) (For reviewing the MoAs of AEDs, refer to Brodie, 2016).

The synergistic effect is an interesting concept but, unfortunately, it has never been clearly demonstrated in clinical practice. Indeed, studies performed in patients on polytherapy showed that suppraadditive adverse effects due to phramacodynamic interactions were more likely to occur when AEDs displayed the same MoAs (Barker-Haliski et al., 2014).

The ideal combination of AEDs in RP should include drugs with unique and different MoA, or one drug with a unique and the other with several MoAs (Brodie and Sills, 2011). Hence, RP may be accomplished by using the SGAEDs (French and Faught, 2009).

However, this new form of polytherapy has not been universally accepted given the absence, in general, of robust evidence of its efficacy (Barker-Haliski et al., 2014; Brodie and Sills, 2011).

AIM

In this article, we aim to compreensivelly review this topic presenting the evidence in favour and against the use of RP for the daily management of RE.

METHODS

A critical analysis of medical literature on the issue was conducted through an independent narrative literature review on PubMed and Medline databases. We selected articles in Portuguese, English, French and Spanish, with no restriction to the date of publication. The search was performed using combinations of the following terms: epilepsy treatment, rational therapy/polytherapy, supraadditive treatment, drug-resistant epilepsy treatment. Cited references within selected articles were also evaluated.

RESULTS

Rational polytherapy. Myth?

A clinical significant "rational" combination of AEDs should provide suppraadditive, synergistic anticonvulsivant effects and additive/infraadditive toxicity. Indeed, when the suppraadditive anticonvulsivant effects are associated with a high toxicity (whenever adverse effects of a synergistic combination also leads to suppraadditive summation) the protective index (defined as a comparison of the amount of a drug causing a therapeutic effect to the one producing toxicity, and determined as the ratio given by the toxic dose divided by the therapeutic dose) may be unchanged or even reduced. Hence, high values of the protective index are preferable to low values, given that a higher dose of the AED would have to be taken to reach the toxic threshold compared with the dose to obtain a therapeutic effect (Brigo et al., 2013).

The concept of "drug loading" (initial higher dose of a drug that is given at the beginning of a course of treatment before dropping down to a lower mainte-

nance dose (equivalent dosages i.e., equal drug loads) may also bring some insight into whether the increased effectiveness of a combination of AEDs (either with the same or different MoAs) is due to an improvement in efficacy or in tolerability. A robust study looking at the monotherapy versus polytherapy focussing primarily on tolerability did not show evidence of differences in overall efficacy and neurotoxicity between the two regimes in which AEDs were started in equal dose loads (Deckers et al., 2001).

Clinical efficacy has been demonstrated by the use of AEDs with the same MoA (Stephen and Brodie, 2002). However, undesirable and avoidable neurotoxic associations may occur or emerge in patients treated with combinations of AEDs with the same MoAs, as between sodium blockers such as PHT, carbamazepine (CBZ), lamotrigine (LTG), or oxcarbazepine (OXC) (Brodie and Yuen, 1997), although results were conflicting. Indeed, an OXC placebo-controlled, dose ranging trial (Barcs et al., 2000) showed a dose-dependent increase in the incidence of premature discontinuations due to AEDs regardless of concomitant AED use. Different MoA for OXC and CBZ were also proposed in this study due to the fact that a large number of patients were already on CBZ and benefited with the addition of OXC. Another more recent, retrospective and observational study with lacosamide (LCM) as adjunctive therapy in uncontrolled epilepsy (Flores et al., 2012) showed that adding LCM to drugs acting on the sodium channel was in general, but not statistically significant, more efficacious compared to adding it to AEs with other MoAs.

From the early experience with SGAEDs, it became clear that the majority of the patients could be controlled by monotherapy, with only less than 4% of them requiring polytherapy (Kwan and Brodie, 2000a; Brodie, 2013). It is uncertain whether this small percentage of success could be attributed to a synergistic effect or to an additive effect of the multiple drugs used.

Previous attempts to prove a synergistic effect in more limited situations have not shown consisting success (Kwan and Brodie, 2000a; Besag et al. 1998). According to the work of Kwan and Brodie (2000a), none of the 11 patients who received add-on treatment after a second drug became seizure-free. In the study of Besag et al. (1998), the authors concluded that toxicity is more likely to occur when LTG is added to CBZ. A reduction of the dose of CBZ usually reduces the toxicity, allowing the dose of LTG to be increased to achieve its maximum effect. Isobolographic analysis from a seizure model in mice also showed lack of synergism between LCM with VPA or PHT (Brigo et al., 2013). Other combinations that revealed no synergism include those between topiramate (TPM) or sodium valproate (VPA) with PHT or CBZ (St Louis, 2009).

Moreover, the results of pivotal studies to commercialise some of the SGAEDs, namely OXC or eslicarbazepine acetate (ESL), failed to prove the principle of RP. In these studies, the addition of CBZ to another AEDs with the same or different MoA, lead to additive efficacy and more side effects (Halasz et al., 2010). In a well-designed, multicentre, parallel-group, open label study looking at this problem, patients with partial epilepsy not controlled by a single AED or sequential AED monotherapy were randomised to alternative monotherapy or to adjunctive therapy. However, again, there was no significant difference between the two groups regarding seizure freedom or retention rate (Beghi et al., 2003).

By looking at the problem in a different way, we might assume that using AEDs with multiple MoAs would be more efficient than using AEDs with only one known MoA. However, recent data on the use of zonisamide (ZNS) versus CBZ (Baulac et al., 2012), or the older study comparing VPA and CBZ (Mattson et al., 1992), showed that CBZ was as effective, or even more effective, than the AEDs with multiple MoAs.

The only evidence for a possible synergism between two AEDs was established for VPA and LTG (Brodie and Yuen, 1997; Pisani et al., 1999), but these two drugs lead to complex pharmacokinetics interactions that may jeopardize a consistent interpretation. Furthermore, the study of Pisani et al. (1999) had a small sample of 20 patients and changes in seizure frequency were analysed descriptively, without formal statistical analysis. Another study (Moeller et al., 2009) with similar limitations due to its retrospective design in which patients were prescribed LTG plus VPA at the discretion of the epileptologist and not in a randomized way, this combination proved to be clinically effective. Furthermore, the adverse effects that occurred were resolved by decreasing the dosage of one of the drugs without seizure exacerbation.

Experiments in the preclinical phase have not conformed to the literature on synergistic clinical efficacy. A review of more than one hundred studies evaluating 536 experimental drug interactions concluded that no single combination of AEDs consistently displayed true synergism (Jonker et al., 2007).

Several reviews have addressed this issue, with the

Table 1. Preclinical synergistic antiepileptic drug (AED) combinations

References	Synergistic combinations of AEDs
Masuda et al., 1981	PB with PHT
Chez et al., 1994	VPA with PHT
Shank et al., 1994	TPM with CBZ and PB
Borowicz et al., 2002	GBP with CBZ, VPA, PHT and PB
Luszczki et al., 2003	LTG with TPM
Cuadrado et al., 2002	VPA with LTG
Luszczki et al., 2005*	TPM with FBM and OXC
Shandra et al., 2013	LCM with CBZ, LTG, TPM, GBP and LEV
Russmann et al., 2016	PER with ZNS

PB – Phenobarbital; PHT – Phenytoin; VPA – Valproate; CBZ – Carbamazepine; GBP – Gabapentin; LTG – Lamotrigine; TPM – Topiramate; FBM – Felbamate; OXC – Oxcarbazepine; LCM – Lacosamide; LEV – Levetiracetam; PER – Perampanel; ZNS – Zonisamide.

* Subadditivity (antagonism) regarding neurotoxicity with OXC and FBM or OXC and LTG.

Table 2. Clinical synergistic antiepileptic drug (AED) combinations

References	Synergistic combinations of AEDs
Rowan et al., 1983	VPA with ESM
Leach, Brodie, 1994	VGB with TGB
Brodie, Yuen, 1997	VPA with LTG
Stephen et al., 1998	LTG with TPM
Pisani et al., 1999	VPA with LTG
Brodie, Munford, 1999	CBZ with VGB or VPA
Perucca, 2006	STP with CLB
Moeller et al., 2009	VPA with LTG
Chung et al., 2010	LCM with LEV
Flores et al., 2012	LCM with AED sodium channel blockers
Brodie et al., 2014	RTG with AED sodium channel blockers or AEDs with other MOAs

VPA – Valproate; LTG – Lamotrigine; ESM – Ethosuximide; CBZ – Carbamazepine; VGB – Vigabatrin; TGB – Tiagabin; TPM – Topiramate; LCM – Lacosamide; LEV – Levetiracetam; CLB – Clobazam; STP – Stiripentol; RTG – Retigabine.

overall conclusion being that RP "remains speculative concerning better efficacy based on the use of AEDs with differing MoAs" (Ben-Menachem, 2014), and that "experimental and clinical evidence in support of it is sparse" (Brodie and Sills, 2011).

As for RP and side effects, there is evidence that adding AEDs with the same MOAs may lead to an enhancement of side effects. "In particular, care should be taken to avoid an excessive drug load, which can be associated with decreased tolerability" (Brodie and Sills, 2011).

It is difficult to drawn reliable information from studies with AEDs with multiple MoAs given the fact that the same MoA might not be responsible for drug efficacy, or toxicity, in different patients. Furthermore, the mechanistic minutia of many available AEDs, with hypothetic contributions to their clinical effects, is still not fully understood. This brings more confusion to the concept of RP as it is mostly based on MoAs (Brodie and Sills, 2011).

Rational polytherapy. Reality?

Most patients with RE take two to three AEDs, some even four or more. Therefore, some rules should be introduced to rationalise their use in order to achieve an optimal outcome. Can RP be a good strategy? In other words, is there evidence supporting RP? The correct response is no. So far, there is no evidence unequivocally validating this form of polytherapy. Nonetheless, strong arguments favouring RP may be found.

According to Kwan and Brodie (2000a), in 2000, 64% of the patients with epilepsy de novo were achieving freedom from seizures with an appropriate monotherapy regimen. Nine years later, this percentage increased by 4.4% (68.4%) through the use of and at the expense of polytherapy regimen (3, 4, and even 5 AEDs) with SGAEDs that had new or different MoAs (Brodie and Bamagous, 2009). Although small, this amount should not be disregarded when addressing RE, and it seems worthwhile considering polytherapy always using at least one SGAED.

Although sparse, there is experimental (Table 1) and clinical (Table 2) evidence in support of RP. Animal models of seizures, epilepsy and drug-related neurotoxicity are ideal to evaluate the efficacy and toxicity of drug combinations in large groups of genetically homogeneous animals. The latter is relevant even if direct transition from experimental data to humans is questionable (Barker-Haliski et al., 2014; Brodie and Sills, 2011). These studies should include: a) efficacy and toxicity models in which both AEDs are at least minimally effective; b) AED ratios reflecting those used in clinical setting; c) concentration analysis of AEDs in both plasma and brain, in order to exclude confounding pharmacokinetic interactions; and d) the use of appropriate methods of analysis, such as isobolography, because they measure effectiveness and determine infra-additive, additive, or supra-additive interactions (Brigo et al., 2013).

Some examples of experimental synergistic combinations of AEDs will follow. The anticonvulsant interaction between PB and PHT was found to be supradditive against maximal electroshock (MES) seizures in mice, but neurotoxicity was not studied (Masuda et al., 1981). Another combination, VPA and PHT, displayed syner-

gism in terms of anticonvulsant effect against MES in the rodent and the neurotoxic activity was simple additive (Chez et al., 1994). A clear-cut synergy was again evident against MES in mice when TPM was co-administered with CBZ or PB (Shank et al., 1994). A distinct synergism also occurred for the combinations of gabapentin (GBP) with CBZ, VPA, PHT and PB (Borowicz et al., 2002). Synergistic combination in terms of efficacy was shown between LTG and TPM (Luszczki et al., 2003), and TPM with felbamate (FBM) and OXC, but subadditivity or antagonism, with respect to neurotoxicity with OXC and FBM or with OXC and LTG was also found in the MES-induced seizures and chimney test in mice (Luszczki and Czuczwar, 2005). The same was found for LCM with CBZ, LTG, TPM, GBP and levetiracetam (LEV) in the 6-Hz seizure model in mice (Shandra et al., 2013).

Nevertheless, with the possible exception of the preclinical synergistic interaction between VPA and LTG (Cuadrado et al., 2002), synergistic combinations identified in animal models do not reliable extend to the clinic (Barker-Haliski et al., 2014). However, experimental studies may be the right way to overcome restrictions imposed by human clinical studies, such as fixed drug doses (which prevent optimal combinations of dosages with the most benefit and least toxicity) (French and Faught, 2009). The first combinations with two AEDs with different MoAs, PB with PHT, proved to be superior in terms of efficacy and/or toxicity when compared to AEDs of similar MoAs, CBZ and PHT (Brigo et al., 2013). These were the initial studies leading to the concept of RP, which evolved with the advent of SGAEDs. Overall, every experimental study stresses the need to use a combined effect of two different pathways rather than a single pharmacological pathway (Brigo et al., 2013). Furthermore, the most successful experimental combination of two AEDs appears to be the one of a single MoA of one AED with a multiple MoAs of the other AED (Deckers et al., 2000). Recently, two widely used SGAEDs – perampanel (PER), a noncompetitive AMPA receptor antagonist, and zonisamide (ZNS), a modulator of voltage-sensitive sodium channels and T-type calcium currents – have shown synergism in the rat amygdala kindling model of temporal lobe epilepsy. This suggests that these two AEDs could be successfully used in focal epilepsies (Russmann et al., 2016).

Combinatorial clinical studies are difficult to undertake. They require the investigation of efficacy and tolerability of both single AEDs and combinations in a homogeneous population of patients with a design powerful enough to be able to separate synergism from additivity alone. Moreover, they also need adjustments of the AEDs combinations to balance overall drug load (Barker-Haliski et al., 2014). The literature claims a particular efficacy for a combination of a sodium channel blocker with either a GABA-ergic (Brodie and Sills, 2011) or a multiple MoAs drug (Kwan and Brodie, 2000b). The only broad evidence of synergism is with VPA and LTG. This was achieved in a trial (Brodie and Yuen, 1997) in patients without seizure control, where an attempt was made to substitute CBZ, PHT or VPA for monotherapy LTG (and in which an adjustment in the LTG dosing schedules for the pharmacokinetic interactions among these AEDs resulting in the same circulating LTG concentrations for all three combinations was performed). The data has shown that the efficacy was strikingly higher in the VPA plus LTG group when compared with the LTG plus CBZ. Detailing a study that has already been mentioned, a trial performed in twenty patients with focal seizures stable on a combination of AEDs, showed that among the thirteen who did not display a good response to the consecutive addition of VPA and LTG, four became seizure free and another four experienced more than a 50% seizure reduction when both drugs were given in combination. This effect was achieved despite lower doses and circulating concentrations than those occurring if administered separately (Pisani et al., 1999).

Other apparent or proved synergistic combinations of AEDs with different MoAs, although based in small samples of patients, small clinical trials or short treatment periods, are VPA with ethosuximide for generalized absences (Rowan et al., 1983), PB with PHT for generalized tonic-clonic seizures (Cereghino et al., 1975), CBZ with vigabatrin (VGB) or VPA (Walker and Koon, 1988; Kwan and Brodie, 2000a; Brodie and Munford, 1999), VGB with tiagabin (seldom used nowadays) for focal seizures (Leach and Brodie, 1994), LTG with TPM for a wide range of seizures (Stephen et al., 1998), stiripentol with clobazam in the severe myoclonic epilepsies of the pediatric population (Perucca, 2006), and azogabine/retigabine with either sodium channel blocking AEDs or with AEDs with other MoAs (Brodie et al. 2014), and LCM with any concomitant AED regimen, including sodium channel blocking AEDs (Chung et al., 2010). However, there is also evidence of a higher reduction in seizure frequency when LCM is associated to AEDs not acting on the sodium channel (Sake et

al., 2010). To investigate whether different MoAs-based AED combination therapies in focal epilepsies are more effective than same MoAs-based AEDs combinations, Margolis et al. (2014) used real-world data from a large sample and showed that the former combinations had greater effectiveness (as measured by treatment persistence and lower risk for hospitalization or emergency department visits).

Finally, "irrational" polytherapy can occur due to several reasons and should be avoided (Brigo et al., 2013). A wrong AED may be chosen for starting a monotherapy regimen leading to an unfavourable event (such as an increase in seizures or toxic side effects). The solution is to replace the first AED by an appropriate one, rather than adding yet another AED. Furthermore, an inadequate knowledge of the MoA of AEDs and their pharmacokinetic and or pharmacodynamic interactions between them may also lead to unexpected or unpleasant symptoms.

CONCLUSIONS

True role of RP in the treatment of the epilepsies is an ongoing topic. The offer of new AEDs with more favourable pharmacokinetic and pharmacodynamic profiles (but, importantly, new or different MoAs), has led to the use of this strategy in clinical practice as an option to increase efficacy. In fact, from the theoretical point of view, it is attractive to think in terms of RP. Although various experimental and clinical investigations have been undertaken, in general they lack robustness and one must be cautions when attempting to apply the conclusions to clinical practice to bring about a synergic anticonvulsant effect in treating a specific epilepsy. However, it must be conceded that there are a few studies with conclusive evidence to support this strategy, the best documented suppradditive effect being the association of VPA and LTG for focal epilepsies. In addition, a greater effectiveness and a decrease of hospitalizations and emergency department visits seem able to be achieved with RP.

At present, RP must be considered as the use of available AEDs to treat seizures types and syndromes, some of unknown aetiology, using the available data of how they interact at the cellular level. Hence, one must admit this approach to be sub-optimal. Accordingly, therapeutic strategy, including the choice of the best combination of AEDs, should be tailored to each patient. However, as a "rational" thought, RP is a strategy worth attempting.

Concepts like efficacy, toxicity, synergism and therapeutic index should be appreciated at the light of the paradigm used to assess drug effects. Further studies are needed and they should focus on: understanding the role of the MoAs in optimizing the control of epilepsies with polytherapy; identification of additional factors that may be crucial for the outcomes when this strategy is implemented, and to the knowledge of the underlying molecular aetiologies of seizures.

CONFLICT OF INTEREST DISCLOSURE

None

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