Egunsola, Oluwaseun and Sammons, Helen M. and Whitehouse, William P. (2015) Monotherapy or polytherapy for childhood epilepsies? Archives of Disease in Childhood . ISSN 1468-2044

MONOTHERAPY OR POLYTHERAPY FOR CHILDHOOD EPILEPSIES?

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Key words: Epilepsy syndromes, antiepileptic drug combinations, young people

Word count: 1615

Background

Antiepileptic drugs were frequently used as polytherapy until evidence from a series of studies in the late 1970s and early 1980s suggested that patients derive as much benefit from monotherapy as polytherapy.[1-3]. Antiepileptic drug polytherapy is increasingly becoming popular again and as much as 30-40% of prescriptions to children are polytherapy.[4, 5]. The availability of new generation AEDs in the last two decades has encouraged polytherapy. AEDs such as lamotrigine, topiramate, levetiracetam, oxcarbazepine, and zonisamide have been approved for paediatric use and are recommended mostly as adjuncts or as second-line agents.[6] Despite the availability of more AEDs, the prevalence of poorly controlled epilepsies still remains the same. About 30% of epilepsies are resistant to treatment.[7] Drug resistant epilepsies almost always require polytherapy, but the question of the best treatment approach when an initial monotherapy fails is still debatable.

Rational polytherapy

Rational polytherapy has been suggested for the treatment of epilepsies. It refers to the use of 2 or more drug combinations with different mechanisms of action. The goal is to achieve synergistic or supra-additive efficacy. A combination regimen is supra-additive when it produces a total effect that is higher than the effects of the sum of individual drugs. Rational polytherapy sometimes aims to attain infra-additive toxicity, such that the component drugs in the polytherapy regimen produce a total toxicity less than the sum of the individual toxicities.[8]

Clinical evidence in support of rational polytherapy for epilepsy is sparse. A 1997 multicentre European study, involving 347 adults, reported synergism between sodium valproate and lamotrigine.[9] Patients given sodium valproate with lamotrigine add-on, had better response rate than those given carbamazepine or phenobarbital with add-on lamotrigine. Another multicentre cohort study in Spain, showed that lacosamide, a sodium channel blocker, was more effective (with a higher seizure freedom rate and clinical response) and better tolerated when combined with a non-sodium channel blocker, rather than with another sodium channel blocker.[10] Neither of these studies however evaluated monotherapy. Synergistic effects however do not always occur when AEDs with different mechanisms of action are combined. Brodie et al, reported that retigabine, a new generation AED which enhances

potassium channel activity, combined with sodium channel or non-sodium channel AEDs showed similar efficacy and safety.[11]

Rational polytherapy requires a sound knowledge of the mechanisms of action of AEDs. A single AED often has multiple mechanisms of action which makes the choice of appropriate combinations challenging.

Monotherapy or polytherapy in epilepsy management

In the late 1970s, Reynolds, Shorvon and colleagues conducted a series of studies which showed that AED efficacy was higher when optimum concentrations of monotherapy were administered to treatment naïve patients. These studies highlighted the fact that polytherapy is unnecessary as an initial approach to epilepsy treatment.[2, 3] This shaped the landscape of epilepsy management afterwards. Recent studies have also demonstrated relatively comparable efficacy and safety profiles for monotherapy and polytherapy. A systematic search of databases Medline and EMBASE using search terms: 'monotherapy' and 'polytherapy or add-on or adjunct*' and 'epilepsy or seizure*' yielded 6 studies in which efficacy and safety of AED monotherapy was compared with polytherapy (Table 1). A French multicentre study, that compared substitution of monotherapy and add-on treatment in patients with failed initial monotherapy, did not show any significant difference in seizure freedom at 12 months, 50% seizure reduction at 2 months, and adverse effect profiles of the two treatment groups.[12] Several other large studies have also reported similar efficacy and safety profiles for substituted monotherapy and add-on therapy after failure of initial monotherapy.[13, 14] None of the six studies showed significant difference in epilepsy control.

When drugs, especially those that share similar metabolic pathways and mechanisms of action are combined, they are likely to interact. In a prospective study, Anderson et al reported a significantly higher risk of adverse drug reactions (ADRs) in children receiving polytherapy than monotherapy.[15] Aggregated safety reports for lamotrigine in children have also shown that the risks of developing most ADRs are lower with monotherapy than polytherapy.[16] Also, supra-additive toxicity is likely with polytherapy involving drugs with similar mechanisms of action. For example, combinations of carbamazepine and oxcarbazepine, or gabapentin and pregabalin, or the use of different benzodiazepines should

usually be avoided. Combinations where the common adverse effects are similar are probably best avoided, at least in the long term. The risk of neurotoxicity is higher when lamotrigine is added to carbamazepine [17] or when lacosamide is co-prescribed with other sodium channel blockers[18], due to pharmacodynamic interactions. Although phenytoin and phenobarbital have different mechanisms, one a sodium channel blocker and the other a gaba-ergic potentiator, their pharmacokinetics interact in complex ways making their interaction rather unpredictable, this makes it difficult to achieve adequate levels without toxicity.

Table 1: Treatment outcome with monotherapy versus polytherapy

			Efficacy			Adverse reactions		
Reference	**Age(yrs)**	**Efficacy outcome**	**Mono**	**Poly**	**P value**	**Mono**	**Poly**	**P value**
†Semah et al, 2014 [12]	18-65	Seizure freedom at 2 months	51%	45%	0.34	-	-	-
		50% seizure reduction at 6 months	76%	84%	0.53	-	-	-
†Millul et al, 2013 [13]	2-86	Treatment failure	27.2%	25%	Ns	29.2%	26.1%	Ns
†Beghi et al, 2003 [14]	2-70	Retention rate at 12 months	55%	65%	0.74	51%	37%	0.07
Deckers et al,2001 [19]	≥18	Seizure freedom at 12 months	86%	74%	-	22%	14%	0.15
†Jozwiak et al, 2000 [20]	12-52	50% seizure reduction at 7 months	53%	50%	-	-	-	-
†Kwan and Brodie, 2000 [7]	1-87	Seizure freedom	17%	26%	Ns	26%	12%	0.25

†Substituted monotherapy versus add-on therapy, Ns-not significant

Treatment approach to epilepsy

The goal of treatment is to achieve full seizure control with minimal toxicity. Therefore, it is important to balance the benefits and risks when choosing AEDs. It is generally agreed that monotherapy should be the initial treatment for newly diagnosed epilepsy in children.[21-23] When one AED does not work, a second drug should be introduced while the child is still receiving the ineffective drug. All changes in therapy, whether adding or withdrawing an AED need to be agreed with the parent and the patient. It is important to consider any possible interactions when introducing the new AED. If seizure control is achieved with the new drug, a gradual withdrawal of the ineffective AED should be attempted. However, withdrawal of the first AED depends on whether it was felt to be partially effective. Also important are its adverse effects and how severe a relapse in the epilepsy would be at the time. For example, in a 16 year old, the period just before important examinations would not be an ideal time to withdraw even a probably ineffective AED.

If the newly added AED is ineffective at maximum tolerated dose (with a serum level at the top of the target range if appropriate) or at a dose well above the maximum recommended dose, one of the AEDs should be slowly withdrawn. A new drug could be introduced either at the same time (placing the child on 3 AEDs temporarily) or after one has been withdrawn.

When polytherapy is inevitable

The cautious delayed withdrawal of a first ineffective AED can be classed a polytherapy, but is generally viewed as sensible, even by staunch advocates of ‘mono-therapy’.

Drug resistant epilepsies

Polytherapy is inevitable in children with drug resistant epilepsies. The International League Against Epilepsy (ILAE) defines drug resistant epilepsy as: ‘failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom’.[24] In children with drug resistant epilepsies, it is common practice to sequentially add AEDs to an existing treatment until seizure control is achieved. However, it is really important to sequentially withdraw ineffective or un-tolerated AEDs, otherwise it is easy to end up with a child on 4 or 5 different AEDs the same time. This increases the likelihood of adverse interactions and more severe

adverse effects. Sometimes, parents are reluctant to withdraw an AED, but can usually be persuaded by knowing that the drug was ineffective and that the epilepsy will vary through better and worse patches irrespective of what is done with the ineffective AEDs. Furthermore, if the plan leads to a worsening in seizures it can always be reversed.

Electroclinical syndromes

There are several electroclinical syndromes, some of which are benign and are easily treated or may require no treatment. However, some electroclinical syndromes will almost always require polytherapy.

Infantile Spasms (West syndrome)

Infantile Spasms not due to tuberous sclerosis are generally treated first-line with either hormonal therapy (prednisolone or tetracosactide) or vigabatrin. Vigabatrin is the treatment of choice in children with infantile spasm with tuberous sclerosis. Emerging evidence from a recent multicentre trial reported that hormonal therapy and vigabatrin combination produces faster clinical response and better seizure freedom than hormonal treatment alone. [25]

Dravet syndrome

Sodium valproate or topiramate is the first-line treatment in children with Dravet syndrome. However, the seizures are often refractory and adjunctive treatment with clobazam and/or stiripentol is usually required.[26] Treatment options are limited because AEDs that target the sodium channel, such as lamotrigine, carbamazepine, oxcarbazepine and phenytoin may aggravate the seizures,[27] and often produce chorea in Dravet syndrome. However some children may in fact benefit from phenytoin.

Lennox-Gastaut syndrome (LGS)

Effective treatment options are few and about 75% of children with LGS have drug resistant epilepsy.[28] Sodium valproate is often combined with one or two other AEDs, including clobazam, or lamotrigine, or rufinamide, or topiramate.[26]

Childhood absence epilepsy (CAE)

CAE usually responds well to treatment with either valproate or ethosuximide, however those with onset under 4 or 5 years of age have a more severe version of CAE,[29] and are typically unresponsive to the usual treatments. However this refractory "Early Onset CAE" can in some cases be well controlled with polytherapy, without adverse effects, even though 3 or 4 AEDs are usually needed, e.g. valproate, ethosuximide, lamotrigine or clobazam.[30]

Conclusion and practical guide

1. Drug resistant epilepsy is a real challenge and it is easy to over treat with excess doses and combinations.
2. Always have a clear and good reason for using polytherapy.
3. Avoid 3 or more drugs at a time (except during tailing off) in ambulant patients if at all possible.
4. Remember to withdraw an AED when it is ineffective.
5. Ensure that all additions and withdrawals of treatment are agreed to by parents and patient.
6. When seizures increase as the dose is reduced, continue tailing it off, unless you are convinced the patient would be better off on it. Remember epilepsy waxes and wanes unpredictably whatever you do.
7. Discontinue an AED if a serious ADR occurs, record it and avoid the drug next time in that patient.
8. Accept that on rare occasions the general advice given here will need to be modified and individualised for a specific child at a specific time in their illness.

Contributorship statement: All authors contributed to the writing of this manuscript and approved the final version**.**

Competing Interests: None

Funding: None

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