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Drug treatment strategies for epilepsy revisited: starting early or late? One drug or several drugs?

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ABSTRACT – There are two popular strategies for current drug treatment of epilepsy; starting early may be better and polytherapy conveys advantages over monotherapy. This review briefly examines if the historical record is much of a guide to determine the clinical value of these two strategies. Great clinical scientists of the 19th and early 20th century, such as Sir William Gowers, and William Aldren Turner, offered vivid single case studies and showed early results of seizure remission in groups of subjects. The historical record offered, however, no evidence of clear clinical benefits for early treatment and polytherapy. Combination treatment was thought to be useful in only some cases. In agreement, current evidence shows no clear clinical benefit of starting treatment early, except perhaps in severe epilepsy. Polytherapy is clinically useful in a subgroup of subjects, but despite being a standard treatment strategy for over one hundred years, it has been poorly studied. In fact, there is no compelling experimental or clinical evidence for a difference in seizure outcome between monotherapy and polytherapy. This surprising finding should prompt a re-appraisal regarding the need to test both strategies separately for the licensing of new antiepileptic drugs.

Key words: lessons from history, drug treatment strategies, starting antiepileptic drugs, AEDs, monotherapy, combination therapy, Sir William Gowers, William Aldren Turner

Two popular strategies for current drug treatment of epilepsy are that treatment may be better started early and that polytherapy conveys advantages in anti-seizure efficacy, referred to as synergy, over monotherapy. This review briefly examines if the historical record is much of a guide to determine the current clinical value attributed to these strategies. In addition, possible implications of the current evidence on single *versus* add-on therapy for regulatory drug trials will be briefly discussed. Famous academic neurologists of the 19th and early 20th century, such as Sir William Gowers, and William Aldren Turner, offered vivid single case studies and showed early results drawn from groups of subjects on seizure remission (Gowers, 1885; Turner, 1903).

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Both perspectives -the scientific and the personal- are indispensable to understand the value of the competing strategies.

The historical record: William Aldren Turner and William Gowers

William Aldren Turner (1864-1945), in his day physician to the National Hospital, Queen Square, and to King's College Hospital, London, was one of the major figures in epileptology in the period between Hughlings Jackson in the latter part of the 19th century and the advent of electroencephalography in the 1930s. Turner (1903) examined the records of the Out-patient Department of the National Hospital for the Paralysed and Epileptic in London covering many years of treatment, mainly with bromides and other medications used at the time. The total number of mostly out-patients was 366 and only 11 came from private sources. Of his 366 cases, 86 showed an arrest of the seizures, defined as a remission of at least two years, ranging from 2 to 25 years. The majority of these patients continued the bromide treatment during the whole period of arrest and Turner thus concluded, with few exceptions, that "the amelioration cannot be described as other than arrest during the administration of the bromides". Although Turner considered many factors such as age, pregnancy, and family history that might affect prognosis, a noteworthy exception was the lack of a mention of whether bromide monotherapy or combinations of medications used at the time made any difference with regards to the number of patients with two-year remission. In the discussion of Turner's paper, one Dr. W.H. Blake noted that the curability of epilepsy was not much greater after, compared to before, bromide treatment. In the third of the Morison Lectures in 1910, which were delivered before the Royal College of Physicians in Edinburgh, AW Turner discussed combining bromides with other agents if bromide alone was not sufficiently beneficial. Without providing numerical outcome results, he noted briefly that "Combinations of the bromide salts, with other remedies, are found useful in some cases". "A combination of a bromide salt with borax has been of service where the bromides or borax, separately", Turner noted, "had been of little use" (Turner, 1903). Turner cautioned that he had not enough experience "to say definitely whether it is better in all cases than bromide alone, but, with two or three exceptions, it has been of great service in diminishing or even arresting fits in cases in which the bromides alone have been of no use" (Turner, 1903). Turner suggested that a combination of bromide and belladonna (which was one of the preferred drug combinations of the pre-bromide era) may be useful in cases of otherwise intractable combined seizure types. Again, he offered no numerical results for comparing single *versus* polytherapy.

As to the influence of delayed treatment, Turner reported that he had seen a greater prospect of arrest or improvement during the first five years than during the second five years of the disease (29.1% remission of at least two years when regular treatment started within one year after the onset of epilepsy, 29.8% within the first three years, 20.4% after three years but before five years, and 11.5% after five years). Turner observed that remission may take place even after a duration of 20 to 30 years (Turner, 1903).

Sir William Richard Gowers, (1845-1915) was a famous British neurologist (Schmidt and Shorvon, 2016) who practiced at the National Hospital for the Paralysed and Epileptics, Queen Square, London (now the National Hospital for Neurology and Neurosurgery) from 1870-1910, ran a consultancy from his home in Queen Anne Street, W1, and lectured at the University College Hospital. He published extensively, but is probably best remembered by those interested in epilepsy for his *Epilepsy and Other Chronic Convulsive Diseases: Their Causes, Symptoms & Treatment*. (Gowers, 1885). Gowers, was apparently not a great provider of data but preferred vivid case vignettes. He noted that "The combinations of bromide with other drugs are of much value in the treatment of epilepsy, in many cases a greater effect is produced by the combinations than by either drug alone" (Gowers, 1885). Gowers, combined bromides with drugs including belladonna, digitalis, atropine, and borax, and astutely noted that cases treated with the combination, without trying either drug alone, were not, as he wrote "strictly to the point although they deserve mention as an account of satisfactory therapeutic results". As for the benefit of starting treatment early rather than late, Gowers, only noted that prognosis was inversely proportional to duration. As Gowers, did not compare the effect of treatment in patients with untreated epilepsy with different duration, his data cannot provide any clarification as to whether delayed treatment was bad for prognosis.

The advantages of early drug treatment: the current evidence

The traditional view in favour of early drug treatment was not convincingly based on the observation of a worse prognosis of epilepsy with longer duration. The historic record was, however, not much of a guide because it did not compare outcome of early *versus* delayed drug treatment in epilepsy of similar duration. There seem to be no randomised clinical trials with experimental animals in which the clinical benefit of early antiepileptic drug (AED) treatment

for acute or chronic seizures has been investigated. The seminal evidence comparing the strategies of early *versus* deferred drug treatment of early epilepsy was established in a large pragmatic trial with a randomised open design. Pragmatism in clinical trials arose from concerns that many regulatory randomised trials did not adequately inform practice, because they were optimised to determine efficacy (Ford and Norrie, 2016). Because regulatory trials were performed with relatively small samples at sites with experienced investigators and highly selected participants, they could be over-estimating benefits and under-estimating harm. This led to the belief that more pragmatic trials, designed to show real-world effectiveness of the intervention in broad patient groups, were required (Ford and Norrie, 2016).

A multicentre, randomised, open trial compared seizure outcome of early *versus* late treatment (Musicco *et al*., 1997). Patients with a first tonic-clonic seizure were randomised to immediate AED treatment or to delayed treatment only after another seizure. Fifty-two (24%) of the 215 patients randomised to immediate treatment and 85 (42%) of the 204 randomised to delayed treatment had a seizure recurrence during follow-up. Of the immediately treated patients, 87% had no seizures for a year and 68% had no seizures for two years, while only slightly fewer patients (83% and 60%, respectively) achieved these endpoints following delayed AED treatment. Patients treated after the first seizure and those treated after seizure relapse had the same probability for one and two-year seizure remission. In summary, AEDs reduce the risk of relapse but long-term remission is not influenced by treatment of the first seizure (Musicco *et al*., 1997). This important result was confirmed and extended to focal seizures in the MRC Multicentre trial for Early Epilepsy and Single Seizures (MESS, 2005). The MESS study showed a reduced risk of further seizures in patients, for whom treatment with AEDs was uncertain, who were randomly assigned immediate treatment compared with delayed treatment (*figure 1*). However, there was no evidence of

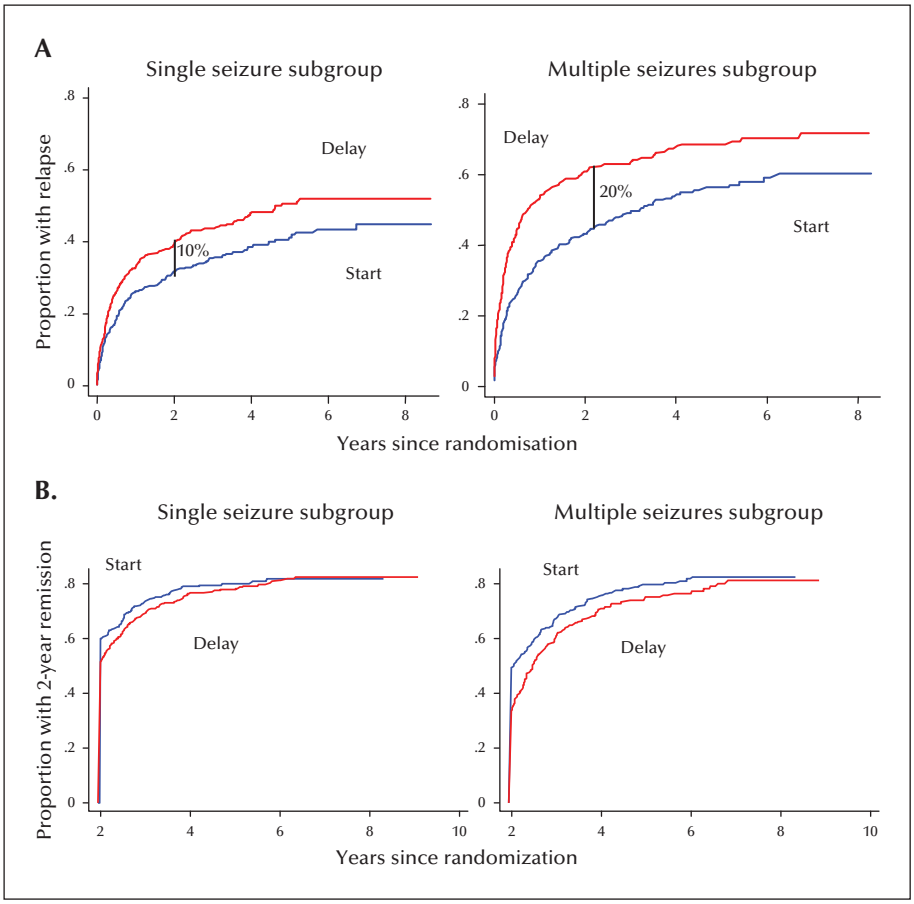

Figure 1. Starting AEDs: early *versus* late? The MESS study showed that although there was a higher relapse rate with delayed antiseizure treatment *versus* immediate treatment (recurrence) (A: time to first seizure), this difference gradually diminished over the years (B: time to two-year remission) (see text for discussion; shown with permission; Marson *et al*. [2005]).

an effect of early *versus* late treatment on long-term remission rates of two years or more. In addition, the two policies did not differ with respect to quality of life outcomes or serious complications. The authors concluded that while immediate AED treatment reduces the occurrence of seizures in the next one to two years, it does not affect long-term remission in individuals with single or infrequent seizures.

In a subsequent analysis, a prognostic model was developed based on individual patient data from MESS to enable identification of patients at low, medium, or high risk of seizure recurrence. Individuals with two or three seizures, a neurological disorder, or an abnormal EEG were identified as the medium-risk group, those with two of these features or more than three seizures as the high-risk group, and those with a single seizure only as the low-risk group. The model shows that there is little benefit in immediate treatment for patients at low risk of seizure recurrence, but potentially worthwhile benefits are seen for those at medium and high risk (Kim *et al.,* 2006). Using stratified Kaplan-Meier estimates of the probability of a future seizure, the absolute risk difference during the first year is 13 percent points (59% *versus* 36%) for those with high risk of recurrence and much smaller for lower risk groups (Kim *et al*., 2006). The clinical significance of the findings is that for most patients who wish to defer drug treatment, this confers advantages including no side effects and no burden of taking drugs every day, for those who are willing to take a 13% risk increase of recurrence. Informed physicians can rely on data and informed patients may choose what they prefer.

The advantages and disadvantages of starting drug treatment following a first unprovoked seizure have been evaluated in six studies (Leone *et al*., 2016). For the two largest studies, data were available for individual participant meta-analysis. Compared to controls, participants randomised to immediate treatment had a lower probability of relapse at one year (RR: 0.49; 95% CI: 0.42 to 0.58), at five years (RR: 0.78; 95% CI: 0.68 to 0.89), and a higher probability of an immediate five-year remission (RR: 1.25; 95% CI: 1.02 to 1.5). However, there was no difference between immediate treatment and control in terms of five-year remission at any time (RR: 1.02; 95% CI: 0.87 to 1.21). Furthermore, AEDs did not affect overall mortality after a first seizure (RR: 1.16; 95% CI: 0.69 to 1.95). Compared to deferred treatment (RR: 1.49; 95% CI: 1.23 to 1.79), treatment of the first seizure was, however, associated with a significantly higher risk of adverse events. Moderate-to-low quality evidence indicated an association with treatment of the first seizure compared to no treatment or placebo (RR: 14.50; 95% CI: 1.93 to 108.76 and RR: 4.91; 95% CI: 1.10 to 21.93, respectively) (Leone *et al*., 2016). In summary, treatment of the first unprovoked seizure reduces the risk of a subsequent seizure but does not affect the proportion of patients in long-term remission. Furthermore, AEDs are associated with adverse events, and there is no evidence that they reduce mortality. In light of this result, the decision to start AED treatment following a first unprovoked seizure should be individualised and based on patient preference as well as clinical, legal, and socio-cultural factors.

Polytherapy *versus* monotherapy: does synergy exist? The current evidence

Around 50% of all patients with new-onset epilepsy enter long-term seizure remission with the first AED given as monotherapy (Kwan and Brodie, 2000). No evidence exists to support polytherapy, *i.e*. the concurrent treatment with two or more AEDs for new-onset epilepsy. The 50% who do not achieve seizure freedom are given other AEDs in a trial-and-error manner, usually as adjunctive therapy or by switching to another monotherapy. This approach is successful in about 30% of cases, leaving around 20% of patients who do not respond fully to several AEDs given alone or in combination. Although polytherapy for those who do not benefit from single drug treatment is the universally recommended standard, there is little information available as to which drugs might work best in combination. Conventional AEDs act by blocking sodium channels or enhancing gamma-aminobutyric acid function. Some newer AEDs have novel mechanisms of action, including impairment of the slow inactivation of sodium channels, binding to the presynaptic vesicle protein SV2A, binding to the calcium channel alpha2delta subunit, and opening select potassium channels. Several AEDs have multiple or uncertain mechanisms of action. The efficacy of new AEDs in animals is not routinely tested with concurrent treatment. Quantitative techniques, such as isobolography, can be used to compare the efficacy and side effects of AED combinations. Assessing supra-additive effects, or synergy, by dose-effect curve addition is far from straightforward, as shown in the early studies in the 1980s. In many studies assessing protection against convulsants causing acute seizures, mostly in rodents, the combination of two AEDs was merely additive, suggesting that polytherapy would not be expected to convey advantages over monotherapy for human epilepsy. This was the case for the following AEDs: *e.g*. phenytoin and phenobarbital (Bourgeois, 1986), carbamazepine and phenobarbital (Bourgeois and Wad, 1984), valproate with phenobarbital or carbamazepine (Bourgeois, 1988a), valproate combined with ethosuximide (Bourgeois, 1988b), topiramate with phenytoin (Shank *et al*., 1994), and tiagabine with either lamotrigine or topiramate (Luszczki *et al*., 2002). Combinations

of tiagabine with either lamotrigine or topiramate were simply additive (Luszczki *et al*., 2002).

Supra-additivity was shown for phenobarbital and phenytoin in mice and rabbits against maximal electroshock, but neurotoxicity of this combination was not studied (Masuda *et al*., 1981). For the combination of valproate and phenytoin against maximal electroshock in mice, the neurotoxic activity was simply additive (Chez *et al*., 1994). A clear-cut synergy was reported for combinations of topiramate with carbamazepine or phenobarbital, gabapentin with carbamazepine, valproate, phenytoin, and phenobarbital (Borowicz *et al*., 2000) and for combinations of lamotrigine and topiramate (Czuczwar and Borowicz, 2002). However, such combinations, with the possible exception of lamotrigine and valproate (Brodie *et al*., 2011), have not been proven to be particularly useful compared to the use of these drugs individually, as treatment for human epilepsy. The fundamental weakness of this study design, in an effort to demonstrate evidence of synergy, is the existence of an alternative or competing explanation for the success of the combination. Simply increasing the daily lamotrigine dose may have been just as good as adding valproate (which increases the serum concentration of lamotrigine). This is why this study is not entirely convincing as evidence of synergy with a combination of both drugs. In summary, then, there is no experimental support for polytherapy over monotherapy and the isobolographic evidence of synergy has not been shown to have translational value in the treatment of human epilepsy.

Polytherapy *versus* monotherapy: does the mechanism of action matter? The current clinical evidence

There is a controversy whether the antiepileptic mechanism of action is predictive of clinical success of individual AED combinations (Brodie *et al*., 2011). It does not seem unreasonable to use a drug possessing a different mechanism of action when an AED fails as a result of poor tolerability or, perhaps more persuasively, lack of efficacy (Kwan and Brodie, 2000). There are claims in the literature for combining a sodium channel blocker with a drug with GABAergic properties (Deckers *et al*., 2000) or one known to have multiple mechanisms of action (Kwan and Brodie, 2000), but what hard clinical evidence do we have in support of so-called rational polytherapy based on combining drugs with different mechanisms of action? The example often quoted as evidence for the usefulness of combining two drugs with different mechanisms of action is that of adding valproate to lamotrigine (Brodie *et al*., 1997). In the interesting study of Brodie *et al*. (2013), responder rates were significantly higher for the group with valproic acid (which inhibits lamotrigine metabolism) than for the patients taking lamotrigine with carbamazepine or phenytoin (both are enzyme inducers which stimulate lamotrigine metabolism). Thus, pharmacokinetic interaction may interfere with synergy and this is a possible explanation to account for the unquestionable success of combining valproate and lamotrigine. Incidentally, seasoned clinicians might add just a small dose of valproate to save money when lamotrigine is more expensive than valproate. Following up on this observation, Pisani and colleagues performed a small crossover study in 20 patients with focal seizures (Pisani *et al*., 1999). Among the 13 patients who did not respond to the consecutive addition of valproic acid or lamotrigine to their existing regimen, four became seizure-free and an additional four experienced 50% seizure reductions when both drugs were given in combination, despite lower doses and lower plasma drug concentrations compared to when administered separately. Other recommended combinations are based largely on anecdotal observations or small studies. These include valproic acid with ethosuximide for absence seizures (Rowan *et al*., 1983), phenobarbital with phenytoin for GTC seizures (Cereghino *et al*., 1975), carbamazepine with valproic acid or vigabatrin for focal seizures (Brodie *et al*., 1999), vigabatrin with tiagabine for focal seizures (Leach and Brodie, 1994), and lamotrigine with topiramate for a range of seizure types (Stephen *et al*., 1998). Brodie *et al*. (2011) conceded that none of these reports can be regarded as any more than observational evidence in support of the mechanistic hypothesis. Supporters of the mechanistic hypothesis point out that combining two drugs with primarily sodium channel blocking mechanisms may not work well. However, subanalyses have often failed to show a difference in response between patients already taking or not taking sodium channel blockers, however, the details are not widely available and it is not always possible to generate useful information about combination strategies using such post hoc analyses (Brodie *et al*., 2011).

Lacosamide has been tentatively singled out as an agent that may work more effectively when combined with non-sodium channel AEDs (Beydoun *et al*., 2009). However, the data are inconsistent and no formal comparisons were performed between subgroups of patients taking or not taking traditional sodium channel blockers (Saké *et al*., 2010).

The role of the mechanism of antiepileptic action in the discovery of drugs for the treatment of epilepsy has been critically reviewed (Schmidt, 2011). More specifically, two questions were addressed. Firstly, has mechanism-driven AED discovery brought us better

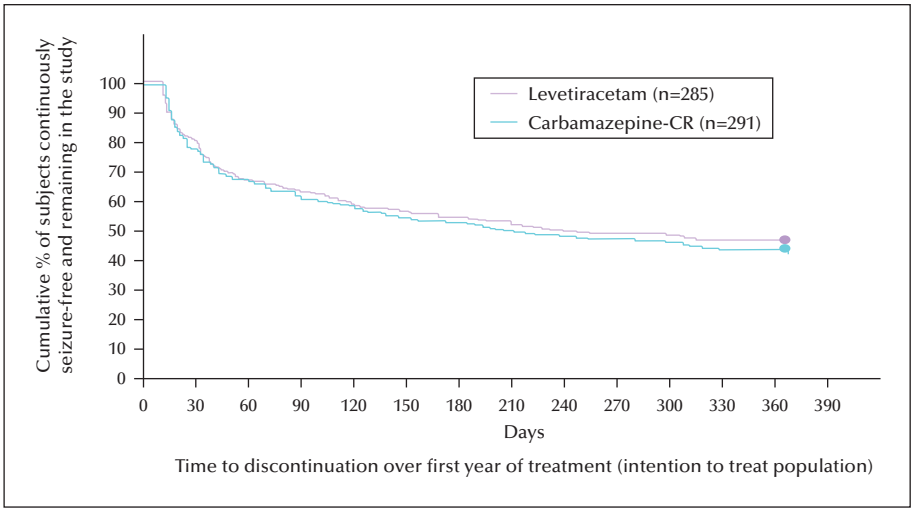

Figure 2. Has our knowledge of AED mechanisms of action so far proven useful in predicting clinical efficacy? The efficacy of levetiracetam monotherapy *versus* controlled release (CR) carbamazepine monotherapy in this randomised controlled trial was very similar. This suggests that clinical efficacy is not primarily predictable based on the primary mechanisms of anti-seizure action which are very different for the two major AEDs (see text for discussion; shown with permission; Brodie *et al*. [2007]).

epilepsy treatment? Although this question is difficult to answer, the short answer is "not yet". Modern AEDs with new or modified mechanisms of action have shown efficacy results that are, at best, indistinguishable from that of older drugs with different mechanisms (Schmidt, 2011). One recent illustration is the virtually indistinguishable drug response seen with levetiracetam *versus* carbamazepine which have different mechanisms of action (*figure 2*). In addition, some modern AEDs, such as progabide, tiagabine, and vigabatrin, have been associated with a number of safety issues. Secondly, why do drugs with new mechanisms seem to have failed to deliver better treatment? Although it is always difficult to understand why a drug does not work, one putative explanation may be worthwhile considering. The past development of new AEDs has targeted putative mechanisms of seizure generation (Löscher *et al*., 2013) As seizures are only symptoms of the underlying epilepsy, blocking seizure generation can provide, at best, only symptomatic treatment. It may be that the failure to treat drug-resistant seizures is related, at least in part, to the failure of current drugs to target the mechanisms underlying epilepsy (Schmidt, 2011). In conclusion, there is a growing concern that continuing to develop new AEDs for drug-resistant epilepsy by targeting seizure generation may be futile and this is one possible explanation for why we do not seem to make substantial progress in drug treatment of refractory epilepsy. Developing AEDs with antiepileptogenic activity may be a clue to better treatment of present-day drug-resistant epilepsy (Schmidt, 2011; Schmidt, 2015).

Clinical implications for combination strategy in drug-resistant epilepsy

Drug-resistant epilepsy has been defined by an International League Against Epilepsy Task Force as "failure of adequate trials of two tolerated, appropriately chosen and used, AED schedules (whether as monotherapy or in combination)" (Kwan *et al*., 2010). Thus, drug-resistant epilepsy can now be readily recognised, sometimes within one year of the diagnosis being made. This should allow earlier referral to specialist centres, and may be used to justify initiation of combination therapy and, most importantly, early evaluation of non-pharmacological treatment options and, specifically, feasibility of epilepsy surgery (Elger and Schmidt, 2008). It is standard to treat patients established on a sodium channel blocker with a drug or drugs that possess different mechanisms of action, such as levetiracetam and pregabalin, or drugs that have multiple mechanisms of action, such as valproic acid, levetiracetam, topiramate, or zonisamide (Brodie *et al*., 2011). However, there is no evidence that any of these drugs is more effective than another, and secondly that any combination is better than monotherapy. If a patient tolerates the first or second drug well with a positive but suboptimal response, combination therapy could be considered, particularly if there is a high seizure density and demonstrable underlying pathology, such as mesial temporal sclerosis or cortical dysplasia (Schmidt and Schachter, 2014). Several duotherapy combinations should be tested before considering the addition of a third drug. Larger numbers of drugs should be avoided as it is unlikely

that this strategy will produce useful seizure reduction (Schmidt and Schachter, 2014).

It has been suggested that combinations of two drugs at low dosage may be better tolerated and, therefore, more effective than a high dose of a single agent (Schmidt and Schachter, 2014), although there is no sound evidence that this is consistently the case. Also, an additional AED may be used not just to treat the epilepsy, but to improve comorbid conditions such as: neuropathic pain (*e.g.* gabapentin, pregabalin), trigeminal neuralgia (*e.g.* carbamazepine, oxcarbazepine), migraine (*e.g.* topiramate, valproic acid), bipolar disorder (*e.g.* lamotrigine, valproic acid), and anxiety (*e.g.* pregabalin, clobazam) (Schmidt and Schachter, 2014).

In summary, and in agreement with Stafstrom (2010), neither such isobolographic methods nor AED mechanisms of action have yet proven useful in predicting clinical benefit in patients (Stafstrom, 2010). The choice of AEDs in patients with epilepsy remains empirical. Putting it bluntly, at present, the experimental basis of polytherapy has little translational value, if any.

Clinical evidence in support of polytherapy *versus* monotherapy

Current adjunctive trial design may provide unequivocal evidence of whether an additional test drug more effectively reduces the number of seizures compared to placebo. This would be adequate to show that adjunctive therapy is effective and conveys therapeutic value. However, routine adjunctive drug trials have not proven useful in predicting clinical benefit of polytherapy over monotherapy. This is simply because the test drug as monotherapy *versus* polytherapy is not compared. As astutely pointed out by Turner and Gowers, evidence is required to show that the clinical benefit of polytherapy is greater than that provided by either of the drugs when used as monotherapy. An ideal trial design for comparing polytherapy *versus* monotherapy would require randomisation of patients with seizures uncontrolled by drug A in one arm, with drug B as an adjunctive, and a second arm as monotherapy (after withdrawal of drug A), and possibly a third placebo arm. Such a complex design has never been performed. Regulatory agencies do not have the legal mandate anywhere to compare therapeutic strategies, and are not, and should not be, dependent on pharmaceutical companies to do this either, since this is not required as evidence for licensing a new adjunctive drug.

Since there are no controlled trials, what is the best evidence that polytherapy is effective compared to prior monotherapy? Historical records give us a clue, and a number of seminal observations were made in the early 1980s. In 94 previously untreated new referrals to a neurological clinic with tonic-clonic or partial seizures or both, the failure rate for optimum single-drug treatment with phenytoin or carbamazepine after a median of 32 months was 17%. This was one of the pioneering studies establishing the clinical value of single-drug therapy for previously untreated patients with epilepsy (Shorvon and Reynolds, 1982) The value of adding a second AED in intractable epilepsy with complex-partial seizures was studied in a long-term prospective trial in 30 adult patients who failed to respond to the maximum use of carbamazepine, phenytoin, phenobarbital or primidone as the first drug (Schmidt, 1982). Based on the individual previous history of one-drug treatment, the most promising AED (carbamazepine, clobazam, clonazepam, phenobarbital, phenytoin, primidone, or valproic acid) was added, if necessary, for clinical benefit and until clinical toxicity occurred. A reduction of the seizure frequency by more than 75% was seen in only four patients (13%) exposed to a second drug when optimal treatment with a single drug failed. The remaining majority of patients (87%) did not benefit from the second drug; in three patients, the seizure frequency increased by more than 100%. The common practice of adding another drug in difficult-to-treat cases may need to be reconsidered until further evidence is presented that two drugs are more beneficial than one drug in the treatment of intractable epilepsy (Schmidt, 1982). This study was prompted by an earlier report by Shorvon and Reynolds (1977), who showed that seizure control had improved in the six months after the introduction of the second drug in only 36%. Seizure control was related to the presence of optimum blood concentrations of at least one drug. The authors warned that much unnecessary polytherapy could be avoided by ensuring an optimum serum concentration of one drug before considering the addition of a second. Since these seminal observations, we have not moved forward much in our insight regarding the relative clinical merits of mono-*versus* polytherapy. Traditionally, AEDs are first tested as adjunctive therapy *versus* placebo for refractory seizures, leading to approval as an add-on treatment. This approach might be followed by monotherapy testing and approval of the monotherapy indication. Efficacy is demonstrated when response to the adjunctive compound is superior to placebo. Current marketed new adjunctive AEDs, however, usually demonstrate weak efficacy; the efficacy exceeds that of placebo with regards to seizure remission (the gold standard of efficacy in epilepsy) in only 6% of patients and a clinical benefit in seizure reduction over placebo of 50% in 21% (Beyenburg *et al.*, 2010).

A prospective multicentre observational study was undertaken on children and adults with epilepsy, in whom initial monotherapy failed, to assess indications

and effects of monotherapy *versus* polytherapy. Patients were followed until 12 months of remission, drug withdrawal, or up to 18 months. Monotherapy and polytherapy were compared for patients' baseline features, indication, retention time, remission, adverse events (AEs), quality of life, and direct and indirect costs. Included were 157 men and 174 women, aged 2-86 years. Of the patients, 72% were switched to alternative monotherapy. Baseline treatment was changed due to lack of efficacy (74%) or adverse events (26%). In total, 243 completed the study (remission: 175; 72.0%). Retention time, hospital admissions, days off work and off school, and quality of life did not differ between the two treatment groups. Patients were followed for 365.3 person-years. A total of 383 incident AEs were reported by 46.4% of patients receiving monotherapy and 40.2% receiving polytherapy (serious AEs: 9.6% *versus* 8.7%; mostly non-drug-related) (Millul *et al.*, 2013).

The value of alternative monotherapy *versus* adjunctive therapy in partial epilepsy refractory to a single AED was determined in two carefully-conducted studies. In a multicentre, parallel-group, open-label study, patients with cryptogenic or symptomatic partial epilepsy, uncontrolled after single or sequential AED monotherapies, were randomised to monotherapy with an alternative AED or to adjunctive therapy with a second AED. The AED to be added or substituted and dose adjustments were determined by the physician's best judgement. Patients were followed until withdrawal from the allocated treatment or for 12 months, whichever first. Outcome measures included the proportion of patients continuing on the assigned treatment strategy, the proportion of patients seizure-free after achieving the target maintenance dose, and rates of adverse effects. Data were analysed by actuarial life tables, Kaplan-Meier survival analysis, and Cox proportional hazard regression model. Of a total of 157 patients (including 94 previously exposed to only one AED), 76 were randomised to alternative monotherapy and 81 to adjunctive therapy. The two groups were balanced regarding clinical characteristics. The 12-month cumulative probability of remaining on the assigned treatment was 55% in patients randomised to alternative monotherapy and 65% in those randomised to adjunctive therapy (p=0.74). The 12-month probability of remaining seizure-free was 14 and 16%, respectively (p=0.74). Adverse effects were similar in the two groups. No significant differences in outcome within or between groups were identified based on aetiology of epilepsy and previous AED exposure. Although these findings should be interpreted with caution due to the low statistical power, as a result of the relatively small sample size, alternative monotherapy and adjunctive therapy were associated with similar outcomes (Beghi *et al*., 2003) (*figure 3*). A second study used a register to determine whether polytherapy with

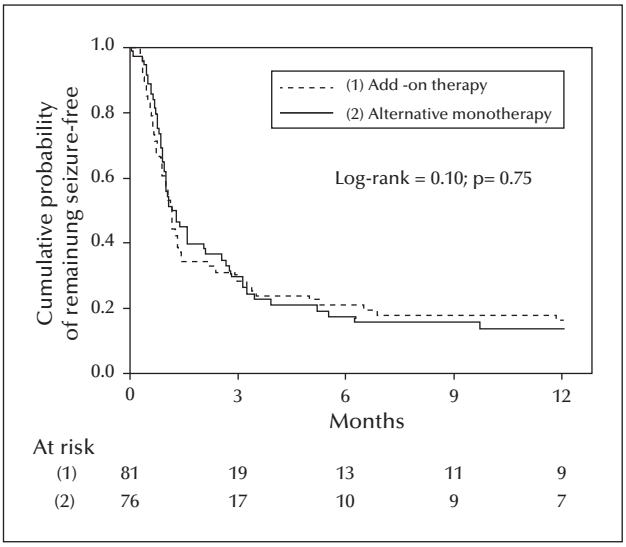

Figure 3. Is add-on treatment more effective than alternative monotherapy for refractory seizures? The cumulative time-dependent probability of remaining seizure-free with add-on therapy *versus* alternative monotherapy in this randomised controlled trial was very similar. This suggests that the add-on therapy does not seem to be substantially superior with regards to clinical efficacy for refractory epilepsy (see text for discussion; shown with permission; Beghi *et al*. [2003]).

AEDs was associated with more adverse effects than monotherapy. Participants were requested to complete the Liverpool Adverse Event Profile (LAEP) in order to quantify adverse effects. Recorded were also type of epilepsy, seizure control, and AED including drug doses. In total, 576 complete data sets were available; monotherapy (n=186), polytherapy (n=325), and control subjects not taking AEDs (n=65). Patients on polytherapy had significantly higher scores on the LAEP than patients on monotherapy. The study authors suggested the importance of discussing with the patient before a second AED is added (Andrew *et al*., 2012).

Do we need separate regulatory studies for monotherapy?

The need for separate regulatory testing for licensing adjunctive AEDs as monotherapy was challenged (Mintzer *et al*., 2015). The authors recommended that the US Food and Drug Administration (FDA) approve adjunctive AEDs in a combined indication for the treatment of seizures or epilepsies, irrespective of concurrent medication use. Why should the traditional separation of monotherapy and adjunctive therapy indications be abandoned? Because, the authors argue, valuable new AEDs, such as levetiracetam, are not labelled for monotherapy in the USA

because of regulatory issues. Many physicians see this restriction as harmful for patients. The authors noted that AEDs are the only drugs in neurology with separate monotherapy and adjunctive therapy indications; that head-to-head comparisons of AEDs in monotherapy, accepted by the European Medicines Agency (EMA) but not by the FDA as evidence of monotherapy efficacy, have not shown significant differences in efficacy; and finally that clinical trials required by the FDA for monotherapy approval are based on ethically and clinically questionable designs. There is no doubt that clarity in the debate about the current monotherapy AED indication, which is strictly tied to the design of monotherapy trials, is urgently needed. The authors justifiably argue that we have no compelling evidence to support the separation of monotherapy and adjunctive therapy indications in epilepsy. Unless, and until, we have such evidence, one must agree with Mintzer and colleagues that there is no basis for a separate monotherapy indication. Furthermore, obtaining clinically relevant evidence of monotherapy efficacy presents formidable challenges. FDA approval of AEDs for monotherapy use was based on unethical and clinically irrelevant trial designs. The use of clinically inappropriate controls, such as substandard doses of other AEDs, rather than an existing gold-standard treatment, prevents the identification of agents with greater effectiveness relative to standard treatment. The FDA seems to have condoned in the past the unethical use of low-dose controls, which deprived patients with frequent seizures of standard treatment for the duration of the trials (Schmidt, 2016a, 2016b). The EMA has a different approach and accepts non-inferiority trials as evidence in the assessment of how much worse a test drug is as monotherapy. However, patients and physicians are primarily interested in significantly better drugs, rather than drugs that are only slightly or no better than available AEDs.

Although we need to resolve the current regulatory bind, it seems premature to justify abandoning regulatory monotherapy trials for future AEDs and, indeed, one should encourage the performance of head-to-head monotherapy studies, whether or not they are required for regulatory approval. New AEDs in the future might bring added clinical benefit compared to older standard AEDs and pass muster regarding the head-to-head comparison. Despite the appealing proposal by Mintzer and colleagues, concerns exist about the approach they advocate. Abandoning conversion to monotherapy trials (as used in the USA) and head-to-head trials (as used in Europe) will lower the bar for future AED approval. Current adjunctive therapy trial design for AEDs is based on comparison of the test drug with placebo. Placebo is an imperfect control treatment because it has never been assessed in comparison with no treatment in epilepsy. The treatment effect of placebo is influenced by many clinical factors that are difficult to control and might distort the effect of the test drug. The most difficult part in this debate is perhaps the question of what the regulatory agencies should do. Giving future AEDs unlimited approval for monotherapy use, based on adjunctive therapy trials, has its problems, as outlined above. If evidence is presented that denying patients valuable new AEDs in monotherapy is harmful, the regulatory authorities might be convinced about the need for change. This most recent debate shows that we are still struggling with the merits and disadvantages of monotherapy and polytherapy as strategies for drug treatment of epilepsy, which is still a public health issue since the ground-breaking initial reports by Gowers, and Turner.

Conclusions and clinical implications

There is a general belief among physicians who treat epilepsy that starting drugs early is better than late and that polytherapy conveys advantages over monotherapy. After reviewing the historical record and the current laboratory and clinical results, we have found no evidence for substantial clinical benefits of early treatment, except perhaps in severe epilepsy. Polytherapy is clinically useful for a minority of subjects but after being a standard treatment strategy for over one hundred years, there is still no convincing evidence from studies in animals or people with epilepsy that it is more efficacious than monotherapy. It is quite sobering that we seem to have made little patient-relevant progress regarding these two major strategies, relative to what astute clinicians demonstrated at the end of the 19th century. This disquieting fact should prompt a re-appraisal on how we treat our patients and, finally, on the need for separate regulatory testing of mono- and add-on therapy for the licensing of new AEDs. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
The authors have no conflicts of interest to disclose.

References

Andrew T, Milinis K, Baker G, Wieshmann U. Self reported adverse effects of mono and polytherapy for epilepsy. *Seizure* 2012; 21(8): 610-3.

Beghi E, Gatti G, Tonini C, *et al*. Adjunctive therapy *versus* alternative monotherapy in patients with partial epilepsy failing on a single drug: a multicentre, randomised, pragmatic controlled trial. *Epilepsy Res* 2003; 57(1): 1-13.

Beydoun A, D'Souza J, Hebert D, Doty P. Lacosamide: pharmacology, mechanisms of action and pooled efficacy and safety data in partial-onset seizures. *Expert Rev Neurother* 2009; 9: 33-42.

Beyenburg S, Stavem K, Schmidt D. Placebo-corrected efficacy of modern antiepileptic drugs for refractory epilepsy: systematic review and metaanalysis. *Epilepsia* 2010; 51: 7-26.

Borowicz KK, Stasiuk G, Teter J, Kleinrok Z, Gasior M, Czuczwar SJ. Low propensity of conventional antiepileptic drugs for interaction with felbamate against maximal electroshock-induced seizures in mice. *J Neural Transm* 2000; 107: 733-43.

Bourgeois BFD. Antiepileptic drug combinations and experimental background: the case of phenobarbital and phenytoin. *Naunyn Schmiedebergs Arch Pharmacol* 1986; 333: 406-11.

Bourgeois BFD. Anticonvulsant potency and neurotoxicity of valproate alone and in combination with carbamazepine or phenobarbital. *Clin Neuropharmacol* 1988a; 11: 348-59.

Bourgeois BFD. Combination of valproate and ethosuximide: antiepileptic and neurotoxic interaction. *J Pharmacol Exp Ther* 1988b; 247: 1128-32.

Bourgeois BFD, Wad N. Individual and combined antiepileptic and neurotoxic activity of carbamazepine and carbammazepine-10,11-epoxide in mice. *J Pharmacol Exp Ther* 1984; 231: 411-5.

Brodie MJ, Yuen AW. for the 105 Study Group. Lamotrigine substitution study: evidence for synergism with sodium valproate? *Epilepsy Res* 1997; 26: 423-32.

Brodie MJ, Mumford JP. for the 012 Study Group. Double-blind substitution of vigabatrin and valproate in carbamazepine-resistant partial epilepsy. *Epilepsy Res* 1999; 34: 199-205.

Brodie MJ, Perucca E, Ryvlin P, Ben-Menachem E, Meencke HJ. Levetiracetam Monotherapy Study Group. Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy. *Neurology* 2007; 68(6): 402-8.

Brodie MJ, Covanis A, Gil-Nagel A, *et al*. Antiepileptic drug therapy: does mechanism of action matter? *Epilepsy Behav* 2011; 21: 331-41.

Brodie MJ, Mintzer S, Pack AM, Gidal BE, Vecht CJ, Schmidt D. Enzyme induction with antiepileptic drugs: cause for concern? *Epilepsia* 2013; 54(1): 11-27.

Cereghino JJ, Brock JT, Van Meter JC, Penry JK, Smith LD, White BG. The efficacy of carbamazepine combinations in epilepsy. *Clin Pharmacol Ther* 1975; 18: 733-41.

Chez MG, Bourgeois BFD, Pippenger E, Knowles WD. Pharmacodynamic interactions between phenytoin and valproate: individual and combined antiepileptic and neurotoxic actions in mice. *Clin Neuropharmacol* 1994; 17: 32-7.

Ford I, Norrie J. Pragmatic trials. *N Engl J Med* 2016; 375: 454-63.

Gowers WR. *Epilepsy and other chronic convulsive diseases: their causes, symptoms & treatment*. New York: William Wood & Company, 1885, 210-11.

Kim LG, Johnson TL, Marson AG, Chadwick DW. MRC MESS Study group. Prediction of risk of seizure recurrence after a single seizure and early epilepsy: further results from the MESS trial. *Lancet Neurol* 2006; 5(4): 317-22.

Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000; 342: 314-9.

Kwan P, Arzimanoglou A, Berg AT, *et al*. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010; 51(6): 1069-77, Erratum: *Epilepsia* 2010; 51(9): 1922.

Leach JP, Brodie MJ. Synergism with GABAergic drugs in refractory epilepsy. *Lancet* 1994; 343: 1650.

Leone MA, Giussani G, Nolan SJ, Marson AG, Beghi E. Immediate antiepileptic drug treatment, *versus* placebo, deferred, or no treatment for first unprovoked seizure. *Cochrane Database Syst Rev* 2016; 5: CD007144 [Epub ahead of print].

Löscher W, Klitgaard H, Twyman RE, Schmidt D. New avenues for anti-epileptic drug discovery and development. *Nat Rev Drug Discov* 2013; 12(10): 757-76.

Luszczki J, Szadkowski M, Czuczwar SJ. Interactions of tiagabine and lamotrigine with new antiepileptic drugs in the maximal electroshock test in mice: isobolographic analysis. *Epileptologia* 2002; 10(1): 7-9.

Marson A, Jacoby A, Johnson A, *et al*. Immediate *versus* deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. *Lancet* 2005; 365(9476): 2007-13.

Masuda Y, Utsui Y, Shiraishi Y, Karasawa T, Yoshida K, Shimizu M. Evidence for a synergistic interaction between phenytoin and phenobarbital in experimental animals. *J Pharmacol Exp Ther* 1981; 217: 805-11.

Millul A, Iudice A, Adami M, *et al*. Alternative monotherapy or add-on therapy in patients with epilepsy whose seizures do not respond to the first monotherapy: an Italian multicenter prospective observational study. *Epilepsy Behav* 2013; 28(3): 494-500.

Mintzer S, French JA, Perucca E, *et al*. Is a separate monotherapy indication warranted for antiepileptic drugs? *Lancet Neurol* 2015; 14: 1229-40.

Musicco M, Beghi E, Solari A, Viani F. Treatment of first tonic-clonic seizure does not improve the prognosis of epilepsy First Seizure Trial Group (FIRST Group). *Neurology* 1997; 49(4): 991-8.

Pisani F, Oteri G, Russo MF, Di Perri R, Perucca E, Richens A. The efficacy of valproate-lamotrigine comedication in refractory complex partial seizures: evidence for a pharmacodynamic interaction. *Epilepsia* 1999; 40: 1141-6.

Rowan AJ, Meijer JW, de Beer-Pawlikowski N, van der Geest P, Meinardi H. Valproate-ethosuximide combination therapy for refractory absence seizures. *Arch Neurol* 1983; 40: 797-802.

Saké JK, Hebert D, Isojärvi J, *et al*. A pooled analysis of lacosamide clinical trial data grouped by mechanism of action of concomitant antiepileptic drugs. *CNS Drugs* 2010; 24(12): 1055-68.

Schmidt D. Two antiepileptic drugs for intractable epilepsy with complex-partial seizures. *J Neurol Neurosurg Psychiatry* 1982; 45(12): 1119-24.

Schmidt D. Antiepileptic drug discovery: does mechanism of action matter? *Epilepsy Behav* 2011; 21(4): 342-3.

Schmidt D. The end of regulatory monotherapy trials? *Lancet Neurol* 2015; 14: 1150-1.

Schmidt D, Schachter SC. Drug treatment of epilepsy in adults. *BMJ* 2014; 348: g254.

Schmidt D, Shorvon S. *The end of epilepsy? A history of the modern era of epilepsy 1860-2010*. Oxford, United Kingdom: Oxford University Press, 2016.

Shank PR, Gardocki JF, Vaught JL, *et al*. Topiramate: preclinical evaluation of a structurally novel anticonvulsant. *Epilepsia* 1994; 35: 450-60.

Shorvon SD, Reynolds EH. Unnecessary polypharmacy for epilepsy. *Br Med J* 1977; 6077: 1635-7.

Shorvon SD, Reynolds EH. Early prognosis of epilepsy. *Br Med J (Clin Res Ed)* 1982; 285(6356): 1699-701.

Stafstrom CE. Mechanisms of action of antiepileptic drugs: the search for synergy. *Curr Opin Neurol* 2010; 23(2): 157-63.

Stephen LJ, Sills GJ, Brodie MJ. Lamotrigine and topiramate may be a useful combination. *Lancet* 1998; 351: 958-9.

Turner WA. A statistical inquiry into the prognosis and curability of epilepsy based upon the results of treatment. *Med Chir Trans* 1903; 86: 259-91.

Further reading

Stafstrom CE. Mechanisms of action of antiepileptic drugs: the search for synergy. *Curr Opin Neurol* 2010; 23(2): 157-63.

Mintzer S, French JA, Perucca E, *et al*. Is a separate monotherapy indication warranted for antiepileptic drugs? *Lancet Neurology* 2015; 14: 1229-40.

Beyenburg S, Stavem K, Schmidt D. Placebo-corrected efficacy of modern antiepileptic drugs for refractory epilepsy: systematic review and metaanalysis. *Epilepsia* 2010; 51: 7-26.

Marson A, Jacoby A, Johnson A, *et al*. Immediate *versus* deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. *Lancet* 2005; 365(9476): 2007-13.

TEST YOURSELF

(1) Is there compelling evidence from clinical studies of animals or humans for a substantial clinical long-term benefit based on early drug treatment of single seizures, which occur early or associated with non-severe epilepsy?(to be validated by the author at the proofs stage).

(2) Is there compelling evidence for a substantial clinical benefit based on combination treatment *versus* switching to alternative monotherapy for the majority of patients with refractory epilepsy?

(3) Is there compelling evidence for a substantial clinical long-term benefit based on combining drugs with different primary mechanisms of action, for the treatment of refractory epilepsy?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".