

## COMBINATION THERAPY SHOULD BE USED AFTER FAILURE OF ONE OR TWO ANTIEPILEPTIC DRUGS (YES)

Over the past 20 years, more than 15 new antiepileptic drugs (AEDs) have been introduced globally many possessing unique mechanisms of action. Despite this plethora of novel agents, outcomes for the common epilepsies in children and adults have not substantially improved, largely because all AEDs are symptomatic anti-seizure and not anti-epilepsy drugs. Three main patterns of response have been identified with just less than 60% of patients having a good prognosis once an appropriate well tolerated AED has been successfully introduced, with another 25% developing refractory epilepsy probably *de novo*. The remainder of the patient population demonstrate a relapsing/remitting course with around half being seizure free at any one time. Very few patients attain remission after failing their first 2 AED schedules particularly due to lack of efficacy. The International League against Epilepsy (ILAE) defines drug resistant epilepsy as “failure of adequate trial of two tolerated, appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom”

If treatment fails at a low dosage due to poor tolerability or following the development of an idiosyncratic reaction, another AED should be substituted. Similarly if the patient documents worsening in seizure control or no useful improvement, another drug, arguably possessing a different mechanism of action, should be tried. However, if there is good response to treatment falling short of seizure freedom with the first or second AED, another drug should be added, again with a different mechanism of action. Attention should be paid particularly to drug burden, which is a function of high dosage as well as number of AEDs.

Different mechanistic groups of AEDs include those affecting the fast and/or slow inactivated state of the Na<sup>+</sup> channel, e.g. lamotrigine, oxcarbazepine and lacosamide, calcium channel blockers e.g. gabapentin and pregabalin, GABA-ergic drugs e.g. clobazam, those that modulate SV2A, e.g. levetiracetam, Kv7 neuronal potassium channels e.g. retigabine, or AMPA receptors e.g. perampanel. Alternatively, the addition of a broad spectrum AED with multiple mechanisms of action can be tried, such as sodium valproate, topiramate or zonisamide.

In clinical practice more than 50 combinations of AEDs have been reported to be successful in individual patients. The approach of combining rather than substituting AEDs in patients with difficult to control epilepsy is more likely to be effective and is a safer option than switching randomly from one drug to another, which carries with it the risk of seizure exacerbation and/or acute neurotoxicity. The most successful duotherapy is lamotrigine with sodium valproate, for which there is good evidence of synergism. There are increasing data supporting the use of AEDs possessing different mechanisms of action in combination. Keeping doses low allows combinations of 2 or sometimes 3 AEDs to be tried in the hope of attaining sustained seizure freedom without unacceptable toxicity. In addition the patient is more likely to retain confidence in their physician if a clear plan of action is laid out early for those who are most likely to have pharmacoresistant epilepsy. The major problem in this setting is the lack of good evidence in support of either course of action in the population at large or for the individual patient and so clinical experience is the driver in this setting.