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Review

Combining antiepileptic drugs—Rational polytherapy?

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ABSTRACT

The global introduction of 14 new antiepileptic drugs (AEDs) over the past 20 years as adjunctive treatment in refractory epilepsy has triggered an increased interest in optimising combination therapy. With a widening range of available mechanisms of AED action, much activity has been focused on the defining and refining "rational polytherapy" with AEDs that have differing pharmacological properties. This paper reviews the available animal and human data exploring this issue. The experimental and clinical evidence in support of "rational polytherapy" is sparse, with only the combination of sodium valproate with lamotrigine demonstrating synergism. Robust evidence to guide clinicians on how and when to combine AEDs is lacking and current practice recommendations are largely empirical. Practical guidance for the clinician is summarised and discussed in this review. In particular, care should be taken to avoid excessive drug load, which can be associated with decreased tolerability and, therefore, reduced likelihood of seizure freedom. A palliative strategy should be defined early for the more than 30% of patients with refractory epilepsy. Nevertheless, the availability of an increasing number of pharmacologically distinct AEDs has produced a modest improvement in prognosis with combination therapy, which will encourage the clinician to persevere with continued pharmacological manipulation when other therapeutic options have been tried or are not appropriate.

1. Introduction

> "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 combination than by other drugs given alone" (William Gowers, 1881)

The modern treatment of epilepsy began with potassium bromide and this drug is still in use to this day.[1] The next effective agent, phenobarbital, was not synthesised until 1911. So what else was Gowers giving his epilepsy patients together with potassium bromide? The list included digitalis, belladonna, cannabis, opium, borax and many other noxious substances. It is well known that Vincent van Gogh benefited from treatment with potassium bromide. He also took digitalis for a period of time. Indeed, he may have been digitoxic when he painted some of the canvases with bright yellow overtones, since digitalis toxicity traditionally distorts colour vision in this way. It is unlikely, but not impossible, that he was taking both drugs together at some point! So if Gowers had many polytherapy options more than 100 years ago, what choices does the modern neurologist have in his therapeutic arsenal for treating drug-resistant epilepsy?

Over the past 20 years, no fewer than 14 antiepileptic drugs (AEDs) have been licensed for use in the common epilepsies and a range of more unusual syndromes (Fig. 1). Of these felbamate (blood dyscrasias and hepatotoxicity) and vigabatrin (concentric visual field defects) are rarely prescribed because of their association with serious adverse effects.[2] Eslicarbazepine is available in Europe, but not in the United States. Stiripentol has been licensed for Dravet's syndrome via the European orphan drug system[3] and rufinamide's usage is confined to seizures associated with Lennox–Gastaut syndrome.[4] Nevertheless, the potential choices of AEDs as monotherapy or in combination are so numerous that it is not possible for a doctor and his or her patient to try every permutation in a single lifetime. Adding the newer AEDS to the established drugs brings their total number up to around 20 for use in the common epilepsies. This allows the possibility of nearly 200 duotherapies or more than 1000 combinations of 3 AEDs!

Most patients with refractory epilepsy take 2, 3 or even 4 AEDs. How then are we to rationalise their usage to provide the best possibility of an optimal outcome? What evidence is there in support of "rational polytherapy"? Conventional wisdom suggests that combining AEDs with different mechanisms of action is more likely to produce seizure freedom than prescribing those with

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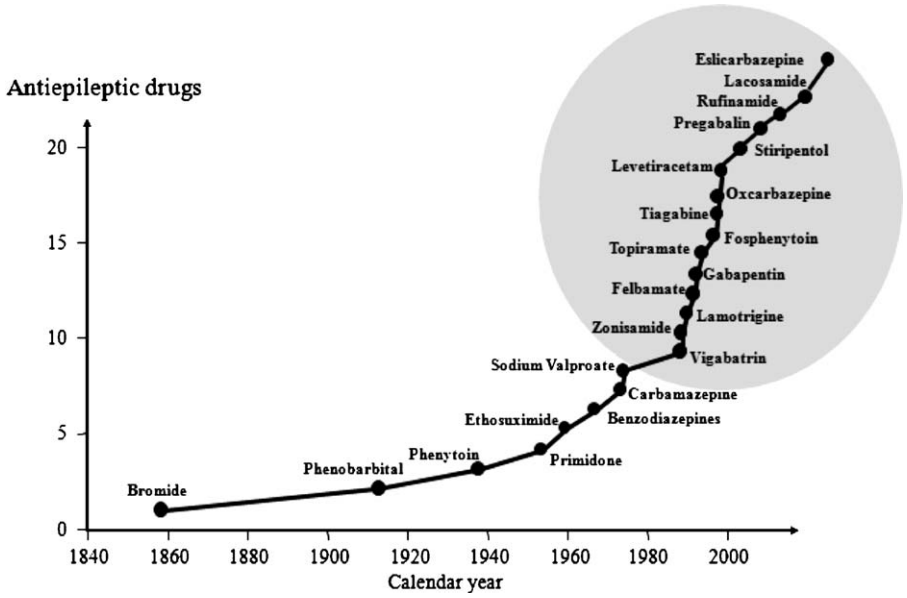

Fig. 1. Chronology of antiepileptic drug introduction over the past 150 years.

similar or overlapping pharmacological properties. It should be remembered too that the spectrum of efficacy for every drug does not always correspond to the license.

2. Pharmacological targets

To best use the range of available AEDs, the prescriber must possess some understanding of what we know about how these agents act in the brain. The knowledge base regarding their pharmacology is limited but slowly increasing. We can now identify a range of mechanisms that differ sufficiently from each other to provide some discrimination in their usage.

Blockade of voltage-gated sodium channels is the most common mechanism of action among currently available AEDs.[5] The established agents phenytoin and carbamazepine are archetypal sodium channel blockers,[6,7] a mechanism they share with the newer drugs lamotrigine, oxcarbazepine, topiramate, felbamate, zonisamide, rufinamide and lacosamide.[8–10] Sodium valproate and gabapentin may also have inhibitory effects on neuronal sodium channels.[11,12] Voltage-gated sodium channels exist in one of three basic conformational states; resting, open, and inactivated. During a single round of depolarisation, channels cycle through these states in turn and the neurone is unable to respond to further depolarisations until a sufficient numbers of voltage-gated sodium channels have returned to the resting state.[13] AEDs with sodium channel blocking properties have highest affinity for the channel protein in the inactivated state and binding slows the otherwise rapid recycling process. As a result, these drugs produce a characteristic voltage- and frequency-dependent reduction in channel conductance, resulting in a limitation of repetitive neuronal firing with little effect on the generation of single action potentials.[14] While most sodium channel blocking AEDs interfere with the fast inactivation pathway, lacosamide selectively influences slow inactivation.[15] Recent evidence suggests that this drug can be usefully combined with sodium channel blockers that act on fast inactivation.[16]

Voltage-gated calcium channels represent another important target for several AEDs.[17] The efficacy of ethosuximide and zonisamide in generalised absence epilepsy is believed to be mediated by blockade of the low voltage-activated T-type calcium channel in the dendrites of thalamocortical relay neurones.[18,19] Sodium valproate may have a similar action.[20] Lamotrigine limits neurotransmitter release by blocking both N- and P/Q-types of the high-voltage-activated (HVA) calcium channel[21] and levetiracetam exerts a partial blockade of N-type calcium currents.[22] Phenobarbital, felbamate, and topiramate are also believed to influence HVA calcium channel conductance, although their effects are less well characterised in terms of channel subtypes or interaction with specific protein subunits.[8,9] Finally, gabapentin and pregabalin also exert their effects via HVA calcium channels. Uniquely, they bind to an accessory subunit, termed $\alpha_2\delta$-1, which can modulate the function of various native channels.[23]

Activation of the ionotropic $GABA_A$ receptor resulting in an enhanced response to synaptically released GABA is a major AED mechanism.[24] Phenobarbital and the benzodiazepines share this effect. They bind to distinct sites on the receptor complex and differentially influence the opening of the chloride ion pore. Typical benzodiazepine-sensitive $GABA_A$ receptors are composed of two α-subunits (α1, α2, α3 or α5), two β-subunits (β2 or β3), and a γ2 subunit, whereas barbiturates are less selective in terms of subunit preference.[25] Barbiturates prolong the duration of chloride channel opening, while benzodiazepines increase the frequency of opening.[26] In addition, phenobarbital is capable of direct activation of the $GABA_A$ receptor in the absence of GABA, an effect which is believed to underlie its sedative properties.[27]

Stiripentol has been identified as a subunit selective $GABA_A$ enhancer with a preference for α3-B3-γ2 containing receptors.[28] Felbamate and topiramate also modulate GABA responses at the $GABA_A$ receptor. While their subunit specificity remains to be established, their binding sites and effects on channel kinetics are reported to be distinct from one another and from those observed with barbiturates and benzodiazepines.[29,30] Finally, levetiracetam can indirectly influence $GABA_A$ receptor function by reducing the negative allosteric modulation of the receptor complex by β-carbolines and zinc.[31]

Vigabatrin and tiagabine exert their actions by selective neurochemical effects at the inhibitory synapse, resulting in altered GABA turnover.[32] Vigabatrin is an irreversible inhibitor of the mitochondrial enzyme GABA-transaminase, which is responsible for the catabolism of GABA, whereas tiagabine prevents the removal of GABA from the synaptic cleft by blockade of GABA transport.[33,34] These distinct mechanisms result in the global