Rational Polytherapy to Patients with Refractory Epilepsy

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The introduction of more than a dozen new antiepileptic drugs (AEDs) over the past 20 years as adjunctive treatment in refractory epilepsy has triggered an increased interest in optimizing combination therapy. However, it has been questioned whether the availability of an increasing number of pharmacologically distinct AEDs has produced a considerable improvement in prognosis with combination therapy. Rational polytherapy is a concept that is predicated on the combination of drugs with synergistic efficacy compared with additional adverse effect. The experimental and clinical evidence in support of ''rational polytherapy'' is sparse, with only the combination of valproic acid 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. Strategies of AED combinations are as follows: (1) Try to avoid combination of AEDs with closely overlapping side effect profiles. (2) Consider AED combinations with evidence of synergistic effect (different or multiple mechanisms of action). (3) Consider patient's characteristics (comorbidity, pregnancy etc.). (4) Be aware of potentially adverse AED interactions, and adjust dosage; monitoring of serum AED concentrations and selection of AED with minimal drug interaction. (5) Titrate new agent slowly and carefully, observe carefully clinical response, and individualize dosage as appropriate (decrease the dose of the original if side effects are encountered). (6) Be prepared to reduce dose of original drug, considering the concept of drug load: establish optimal dose of baseline agent. (7) Try range of different duotherapies. (8) Replace less effective drug if response still poor. (9) Add third drug if still sub-optimal control. (10) Remember that it may be possible to discontinue gradually the previously administered AED(s) in many patients responding to polytherapy. (11) Review the record for searching insufficient polytherapy trials. (12) Devise palliative strategy for refractory epilepsy (never at earlier stage of drug refractoriness): best combination regimens in the past. (13) Consider surgical option at any time.

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