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*Review*

# Single and in combination antiepileptic drug therapy in children with epilepsy: how to use it

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**Abstract:** Treatment of childhood seizures is a pressing challenge within neuropediatrics because of its severe impact to the children and families affected by these debilitating disorders. It is of upmost importance to make an early diagnosis, to start a promptly treatment, to use therapy and dosage of the drug appropriately, based on the specific epileptic type and epileptic syndrome. Single therapy with appropriate dosage is the main approach to treatment. When the drug is the cause of an idiosyncratic reaction it is advisable to replace the suboptimal seizure response with another antiepileptic drug, combined therapy with two antiepileptic drugs is also a viable option. In childhood, polytherapy using more than two antiepileptic drugs remains controversial because the harm of interaction with deleterious drugs could potentially replace the damage caused by the seizures themselves. The use of three or more antiepileptic drugs should be limited to epileptic seizures that are particularly resistant to drugs and when non-drug antiepileptic therapies have failed. An approach to the difficult topic of epileptic treatment in childhood is reported. Key point: mono vs polytherapy in epileptic children; single and alternative therapy in epileptic children; use or three or more AEDs in children.

**Keywords:** epileptic seizures; antiepileptic drugs; children; side-effect

## 1. Introduction

Epilepsy is one of the most frequent medical problems that affect infants and children. Epilepsy and the conditions that cause epilepsy impact children and their families in many ways, influencing cognition, behavior, and socioeconomic status [1]. The incidence of seizures in childhood is higher than during late childhood and mid adolescent and similar to rates reported in adults [2,3]. Over the past two decades several new antiepileptic drugs (AEDs) with improved tolerability profiles and fewer off-target and interaction based side-effects have become clinically available; however, the older, more established drugs are still widely employed [4]. The mechanism of action of AEDs is complex and vary according to the compound. Most act by increasing the inhibitory effects of γ-amino-butyric acid (GABA) properties or reducing the excitatory effects of glutamate by targeting various cellular receptors (e.g. sodium channel blockers) [4,5]. Brodie and Sills [6] report on the different mechanisms of the most employed AEDs. They distinguished six different mechanisms fitting for combination therapy: (a) sodium channel blockers: including phenytoin, carbamazepine, lamotrigine, oxcarbazepine, eslicarbazepine and lacosamide; (b) calcium channel blockers that affect low-voltage activated channels e.g. ethosuximide and those that target high voltage activated channel, e.g. gabapentin and pregabalin; (c) GABA-ergic drugs that increase the duration of chloride channel opening, e.g. barbitures and benzodiazepines, and those that inhibit GABA-transaminase, e.g. vigabatrin and synaptic GABA reuptake blockers, e.g. tiagabine; (d) synaptic vesicle protein 2 A modulation, e.g. levetiracetam; (e) inhibition of carbon anhydrase, e.g. acetazolamide; (f) compounds with many pharmacological targets, e.g. sodium valproate, topiramate, felbamate, rufinamide, zonisamide. Nonpharmacological therapies are also being developed and gradually integrated into disease-management strategies; for example, ketogenic diet, resective surgical interventions or surgical implants, vagus nerve stimulator and responsive neurostimulator. Given the existence of several inherited forms of epilepsy and genetic disorders with epileptic symptoms, gene therapy may potentially revolutionize the treatment of this neurological disorder.

The causes of seizures in children varies greatly and their presentation is often associated with severe morbidity such as cerebral palsy, developmental delay, intellectual disability and abnormal behavior. Additionally, malformations, dysmorphisms, microcephaly, and macrocephaly can be associated with seizures, which can interfere with lifestyle and with pharmacological and non-pharmacological therapeutic responses in affected children. Brain anomalities can precede or follow seizures onset, thus further complicating the already complex course of epilepsy management [2].

## 2. Search procedure

The check was completed on three medical electronic databases (PubMed, Cochrane Library and Scopus Web of Science) by three authors (P. P., G. C. and L.M.) from 30 November 2018 till 300 December 2020. The search string was as follows: “single” and/or “combined” and/or “antiepileptic drugs” [7].

### *2.1. Selection criteria and data extraction*

Qualified studies for the present narrative review were performed exploring databases selecting with a screening of the titles and abstracts through the following inclusion criteria: time (publications

in the last 10 years), language (written in the English language), journal (studies published in specialized journals reporting clinical or pre-clinical results). Exclusion criteria were articles written in other languages, studies involving rehabilitation or psychotherapy, studies with surgery as primary approach or systematic review involving a similar topic. In addition, studies with no accessible data or no accessible full text were excluded. We also excluded all of the remaining duplicates. The study selection and the data extraction were performed independently by four authors (C.O., S.S., G.C., G.G.), and any divergences were resolved by discussion amongst the authors. The senior investigator (R.F. and P.P.) were consulted to revise the entire performance [7].

### *2.2. Statistical methods and analysis*

Due to the discrepant nature of the studies and the lack of controlled studies, it was not possible to carry out metanalysis and statistical analysis. Instead, a descriptive summary was made.

### *2.3. Materials and methods*

We selected from a total of 85 articles published in PubMed, 23 works, by selecting with the research phrase "single and combined antiepileptic drugs children". We focused our search by selecting the terms "single" and "combined" and "antiepileptic drugs". No other similar terms or synonyms such as monotherapy and/or dualtherapy have been used during our research. We also selected articles deal with the ketogenic diet. We selected only English articles which performed studies mainly on pediatric population. We obtained and confirmed data by investigating each one author the validity of every single study. The study was approved from AOU Policlinico–Vittorio Emanuele from Catania with the protocol number VP0013442. Unfortunately, most of the paper was done in adulthood, however we tried to focus our attention on children and organized the results into three subgroups of children undergoing AEDs: monotherapy, polytheraphy and combination therapy.

## 3. Results

During our narrative review, given the limitations of the available database, we are unable to draw a conclusion, but we try to give suggestions that are not specific recommendations. The recommendation for children to replace a different AED instead of adding a second drug when the first is ineffective or causes adverse effects is an over-generalization; the specific recommendation depends a lot on whether the problem is the lack of efficacy or the adverse effects; overall decisions should be based on the type of epilepsy, secondary clinical manifestations and vulnerability to various adverse effects, but specific recommendations about how to make these factors operational in decision-making are very few. We do not mentioned about phenobarbital (the most common drug used in neonatal seizures until now) because was beyond the scope of our article and also because we think that will be useful in next future the shift versus other new AEDs like Lev (Leviretacetam instead of Phenobarbital) [8,9]. The use of non-drug therapy (keto diet, vagal nerve, surgery) also went beyond the scope of our document. It is also difficult to say when to start a non-pharmacological therapy in these studies, which would provide a better judgment on the efficacy of mono or combined treatment. Of course, the physician considers many factors when prescribing an AED, such us: type of seizure, any other medical diagnoses, age and gender, potential side effects of

a drug, interaction of the AED with other medications that the patient can take, pregnancy or going to get pregnant.

Vagus nerve stimulation therapy (VNS) is a treatment designed to prevent seizures by sending regular, small pulses of electrical energy along the vagus nerve to the brain. These pulses are supplied by a device like a pacemaker for the heart (which is why the VNS is sometimes referred to as a pacemaker for the brain). The VNS device is implanted by a surgeon under the skin on the chest wall. A wire runs from the device to the vagus nerve in the neck, part of the autonomic nervous system. VNS therapy can improve seizure control and quality of life for some individuals over time [2–12].

The Ketogenic Diet is a special high-fat, low-carbohydrate diet that helps to control seizures in some persons with epilepsy. It requires careful measurements of calories, fluids, and proteins. "Ketogenic" refers to the production of ketones in the body (keto = ketone, genic = producing), which are formed when the body uses fat for its source of power. Usually, the body uses carbohydrates for its fuel, but because the ketogenic diet is very low in carbohydrates, fats become the primary fuel instead. The Ketogenic Diet should be prescribed by a doctor and carefully monitored by a dietician. Doctors typically recommend the ketogenic diet for children or adults whose seizures have not responded to multiple seizure medications. Several studies have demonstrated that the ketogenic diet can moderate or prevent seizures in some children whose seizures were not well controlled on AED therapy. Ketogenic diet in compound shows us that the plasma levels of Valproic Acid and Phenobarbital, either as monotherapy or in combination, do not change remarkably during the first month on diet, so adjustments in the quotidian dose of these drugs before the beginning of the diet do not therefore appear to be justified [5–12].

Brain surgery is another therapeutic option for individuals who have seizures which cannot be controlled with medication or other forms of treatment. Although surgical procedures for epilepsy have been used for more than a century, the use of surgery dramatically increased in the 1980s and 90s, reflecting its effectiveness as an alternative to seizure medicines for patients with refractory seizures. Not all patients are candidates for surgery. The benefits of surgery should be weighed carefully against its risks, and extensive testing is necessary prior to surgery. Epileptologists work together with neurosurgeons, neuropsychologists and neuroradiologists to review each individual case prior to deciding about surgery.

Medical use of cannabis, now legalized in many countries, has provided promising early research results in treating those living with epilepsy. As a result, the FDA has recently approved the first drug comprised of an active component derived from cannabis to treat rare, severe forms of epilepsy. People living with uncontrolled seizures who have previously attempted other forms of treatment have reported beneficial effects and reduced seizure activity, especially with cannabis derived Cannabidiol (CBD) oil [8–12]. However, individuals should be cautious in arriving at an informed treatment decision and discuss this treatment option with their neurologist/epileptologist.

### *3.1. Monotherapy*

In children, monotherapy with appropriate dosage is the main approach to treatment and is employed with successful in about 50% of children with epileptic seizures. Its use is sufficient to render seizure free the children for at least 12 months [3,5]. The failure of the response to the treatment of the seizures may depend on several factors: the choice of AED, that should be used taking in consideration the diagnosis of the epilepsy type and the epilepsy syndrome, the cause of the

brain dysfunction, the prescription of appropriate dose and the compliance of the children and their parents to the drug administration. This last point is particularly important in the treatment of epileptic children. The disturbances associated to seizures must also be recorded. When the first drug causes idiosyncratic reaction, cutaneous rash or suboptimal frequency of seizures, or adverse effects such as drowsy, insomnia, weigh, gain, mood stabilizing, substitution, or combination of the first drug with other AEDs is required. In children, substitution (alternative) AED is the advisable option. The introduction of alternative drug should be taken place by a gradual reduction of the first drug until the total suspension. The use of the alternative treatment may result in a reduction of frequency of seizures in about 15% of patients [4]. Stephen and Brodie [8], in response to the initial institution of the monotherapy distinguish the outcomes of epileptic patients in four groups: a group of patients, the majority (60%) show a good outcome in a short time with a modest or moderate dose of a single AED, the patients present with a long-term seizures freedom and not notable side effects; another group, a small side of these patients, shows to have suboptimal response to seizures or intolerance to the drugs and must recur to alternative drugs; another group may present with chronic seizures or periodic of remission; the remaining group about 25% is part of the refractory epilepsy [8].

### *3.2. AEDs in combination*

In childhood, failure of the treatment of seizures with the first AED or failure of AED used in alternative, a combination of two AEDs has been successfully proposed. Combination therapy is advised when the response to the initial treatment to first or to the alternative AED is well tolerated by the affected child, but the clinical response is poor or not optimal or when there is evidence of idiosyncratic reactions to the drugs [8,9]. The choice of adjunctive AED is informed by their potential interaction behavior and requires great care because the likelihood of side effects is increased in case of combination therapy. The combination of pharmacologically active compounds can induce three distinct effects: (a) association of two molecules having an extra effect that is the clinical answer of the two AEDs is double as the drugs were administered singularly; (b) the association of the two molecules with an effect infra-additive or antagonist; (c) the association of the two molecules which have an effect supra-additive or synergic [9]. The choice of the AED in combination requires their best clinical efficacy, a broad spectrum of action, different adverse effects profile, and their use in relationship to the associated morbidities.

The ideal adjunctive AED is highly efficacious, has a broad spectrum of action, varies from the previous AED in terms of potential adverse effects, and aligns with any associated morbidities. Broad-spectrum efficacy has been attributed to topiramate, levetiracetam, lamotrigine, valproate as these are effective against a range of epileptic syndromes. On the other hand, zonisamide, felbamate, clobazam are most effective toward treating specific forms of epilepsy and epileptic syndromes (e.g. Lennox-Gastaut syndrome, primary generalized tonic-clonic seizures) [10,11]. For combination therapy to be successful, the adverse outcome profile of each AED must be throughly considered. Side effects are more frequently reported after the use of lamotrigine, carbamazepine, oxcarbazepine, and phenytoin. Treatment with valproate, carbamazepine, phenytoin confers increased risk of liver disorders and with phenytoin, carbamazepine, clobazam tendency to sedation. Side effects associated with the use of topiramate, phenytoin, and zonisamide include concentration loss and cognitive disturbances, while valproate, pregabalin, and gabapentin can cause weight gain [10,13]. Furthermore, some AEDs may have opposing effects: drowsiness vs insomnia; weight gain vs loss;

mood stabilizing vs destabilizing [12]. Moreover, AEDs can have different pharmacokinetics (e.g. whether metabolized by the liver or not) and, as such, will interact with each other differently.

The most promising strategy toward successful combination therapy seems to be choosing AEDs with different mechanisms of action and distinct pharmacological proprieties [2,5]. This conclusion is supported by the research of Brodie and Yuen [11] in 347 patients with various types of epilepsy. The failure of sodium valproate, carbamazepine, phenytoin, and phenobarbital monotherapy was followed by treatment with these drugs individually combined with lamotrigine. The best response was seen in patients treated with lamotrigine and valproate, with 64% of patients responding, compared to lamotrigine and carbamazepin (41%) or lamotrigine and phenytoin (38%). These results were obtained from both patients with partial and tonic-clonic generalized seizures. Good synergy between valproate and lamotregine was also reported in this study using lower median doses of valproate and lamotrigine compared to their singular use and when used in combination with other AEDs [11]. In a study [13] with an open, response-conditional crossover design performed in 20 patients affected by refractory, complex partial seizures, valproate and lamotrigine were evaluated alone and in combination. A 50% reduction in seizure frequency was seen in three of the 20 (15%) patients treated with valproate and in four of the 17 (23%) patients treated with lamotrigine. Among the 13 patients treated by combination therapy, four became seizure-free and nine experienced an average seizure reduction of 62–78%. A study [2] performed in 396 adult patients with focal epilepsy was performed ten years later to evaluate the efficacy of newly developed drugs. The results revealed that a higher percentage of patients achieved a seizure-free outcome (117 of 396; 30%) than in the previous study (22%) ($p = 0.042$). Eighty-three of 218 (38%) patients receiving drug-therapy became seizure-free (compared to 27% in the previous study); of the 151 receiving triple therapy, 30 individuals (20%) became seizure-free (compared to 10% in the previous study). Taken together, these studies indicate that the drugs developed in the last decade, when delivered in combination are more effective in terms of seizure remission (8% increase in overall patient response rate after 10 years). Valproate-lamotrigine, lamotrigine-topiramate, and ethosuximide-valproate co-treatments have proven effective for specific epileptic syndromes. Five patients with absence seizures [14] were monitored for 24-hours using cable telemetry EEG recording, closed-circuit televisions, and serum samples. All of the patients treated with ethosuximide (ETS) in combination with valproate became seizure-free. The combination of lamotrigine and topiramate enhanced seizure control in various forms of epilepsy [15]. In a large study conducted by Joshi et al. [16], 697 patients with either general (n = 386, 55.4%) or focal seizures (n = 331, 44.6%) were treated by monotherapy (n = 264, 37.9%), combination therapy with two AEDs (n = 243, 34.9%), or polytherapy with three or more AEDs (n = 190, 27.2%). In terms of the average AED load, duration of treatment, and adverse event profile (AEP) score, no significant differences were found between the mono and combination therapy. However, significantly higher levels of adverse effects and lower seizures control were seen in the group of patients receiving the polytherapy compared to the other two groups. The incidence of adverse events was increased by combination therapy (relative to monotherapy) and these included headaches, blurred vision, dizziness, irritability, tremor, memory problems, appetite loss, fatigue, hair loss, and slurred speech. Recently, Rosati et al. [17], with a network meta-analysis, report on 46 randomized clinical trial involving 5652 individuals treated with various antiepileptic drugs compared to placebo. In recently diagnosed focal epilepsy, the best results were obtained with carbamazepine and lamotrigine as well

as in refractory focal epilepsy, with levetiracetam and perampanel compared to placebo. Regarding the absence seizures, ethosuximide and valproate were more efficacious compared to lamotrigine.

### *3.3. Polytherapy for pharmacoresistant epilepsy*

Pharmacoresistant epilepsy is defined by the failure to achieve seizure remission for at least one year after treatment with at least two well-tolerated and well-chosen AEDs [18]. In polytherapy employing 3 or 4 drugs, levetiracetam and clobazam are two of the most advised AEDs [2]. The use of three or more AEDs toward combatting pharmacoresistant epilepsy is common in adults and has been reported to be efficacious for seizure control [19–21]. The reaction to each drug is individual and specific and, therefore may respond better to three or more AEDs depending on the type of epilepsy or epileptic syndromes, the adverse effects associated with each AED, and the clinical manifestations presented in conjunction with the seizures. While AED combination therapy has generated positive results in terms of ameliorating seizures, the frequency and severity of the side effects tend to increase proportionately. In children, given the associated risks, combination therapy with 3 or more AEDs should be limited to specific disorders, for example, childhood epileptic encephalopathies. These are age-dependent brain disorders characterized by severe epileptic events, early-onset, persistent encephalographic abnormalities, drug-resistant seizures in various forms, and cognitive involvement [22,23]. In most of the cases, conventional AEDs and polytherapy with 3 or more drugs are unable to prevent the brain damage incurred by the cerebral disorder but may serve to partially reduce seizure frequency. However, the general consensus in neuropediatrics is that the treatment of severe epileptic encephalopathies in children with 3–4 drugs in combinations should be limited to specific situations as this topic requires further optimization [22–26].

Both seizures and AEDs can severely impact the brain, cognitively and developmentally. In children, polytherapy with three or more AEDs should be avoided because the potential damage from the combination of many AEDs could be greater than that caused by the seizures themselves and likely outweighs the benefits of treatment, particularly when the manifestations are not so frequent. A large body of evidence now indicates that the improvements to patient outcome and quality of life do not warrant incurring the increased risks associated with polytherapy, particularly in young children [24]. For childhood focal seizures, first-line monotherapy recommended. Alternative monotherapy includes carbamazepine or valproate, and as coadjuvant therapy [27].

### *3.4. Autistic spectrum disorders*

The etiology of ASD involves complex interactions of immunological, genetic and environmental factors [28]; thus, the use of AEDs is debated and is different case for case. ASD can also be divided into both idiopathic and non-idiopathic (syndromal) forms. Syndromal forms of ASD are characterized by an identified genetic cause and include Prader-Willi Syndrome (PWS), Tuberous-Sclerosis Complex (TSC), Angelman Syndrome and Fragile X syndrome. By studying treatments in established subgroups of ASD, we will define the therapeutics response before applying it to a larger diversified population [29]. Endocannabinoids and Ketogenic [11,12,29] diet began a more conventional therapy in these children, although more study need to be done to specify this matter.

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**Conflict of interest**

All the authors declare that there are not biomedical financial interests or potential conflicts of interest in writing this manuscript.

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