Review of Childhood Absence Epilepsy and Antiepileptic Medications

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ABSTRACT
Epilepsy is a common neurological disorder that disrupts the function of the central nervous system. Childhood absence epilepsy (CAE) is a form of epilepsy that happens nearly exclusively in children aged 3 to 10. Ethosuximide, valproic acid, and lamotrigine are three antiepileptic medications traditionally used by clinicians to treat CAE. Historically, the syndrome has often been dismissed as "harmless" owing to a common "benign" long-term prognosis. Over recent years, the deceptively nonmalignant nature of CAE has been increasingly questioned and reviewed, specifically with respect to how various treatments impact the development and life quality of affected children. This article summarizes and reviews the effectiveness, weaknesses, and potential neurocognitive effects of the three drugs of choice for CAE management and treatment based on existing literature. Multiple studies have suggested that ethosuximide is the optimal initial empirical treatment, producing superior results to valproic acid and lamotrigine vis-a-vis efficacy and tolerability. That being said, valproic acid and lamotrigine are both effective anticonvulsants and are sometimes preferred over more appropriate choices on a case-by-case basis.

Keywords: *Epilepsy, Childhood Absence Epilepsy(CAE), Ethosuximide, Valproic Acid, Lamotrigine, Antiepileptic Drugs(AEDs).*

1. INTRODUCTION

Epilepsy is a neurological disorder characterized by recurrent seizures, whereby abnormal discharges of neurons cause sudden and brief unusual activities in a section of the brain (focal) or the entire brain (generalized). According to the World Health Organization, it is a fairly common disorder affecting 50 million people worldwide. With a variety of factors contributing to the underlying mechanism of epilepsy, its etiology still remains elusive approximately half of the time [1]. Common causes range from genetic and congenital brain abnormalities such as anoxia at birth to various types of damage to the brain later in life, including infections, strokes, toxicity, or changes in the metabolic and immune system. While anyone can develop epilepsy regardless of gender, age, racial or ethnic background, diagnoses may be more common among young children and older adults.

Childhood absence epilepsy (CAE), also known as petit mal seizures, is one of the most common epileptic pediatric syndromes, affecting children aged 3 to 10. An official diagnosis is obtained following an electroencephalogram and an evaluation by a professional clinician. The underlying mechanism causing the syndrome has not been conclusively identified. CAE is regarded as a self-limited epilepsy disorder as the vast majority of patients eventually enter remission, with the exception of approximately 5-10% experiencing variant forms of seizures resistant to treatment [2].

Currently, ethosuximide, valproic acid, and lamotrigine are usually the drugs of choice for children diagnosed with absence epilepsy in terms of efficacy as well as tolerability. However, the adverse neurological effects that follow are generally understudied. Although the prognosis is generally good as children tend to outgrow the condition, the frequency of occurrence of such seizure episodes as high as a hundred times a day could greatly interfere with the child's attention and learning abilities, resulting in poor psychological and cognitive consequences. Up to today, investigations still fall short when it comes to CAE's profound cognitive, psychological, and behavioral repercussions for diagnosed children [3]. This essay reviews in depth the three primary types of antiepileptic medications used to

treat children with absence seizures with regard to each drug's mechanism, strengths and weaknesses, and potential adverse effects specifically related to children's neurocognitive/psychological development. The essay addresses the overemphasis on seizure freedom widely seen in the field today—often at the expense of the affected children's health-related quality of life—and underscores the importance of strategizing treatments with the goal of minimizing the negative impact of medications on epilepsy patients' daily functioning and wellbeing.

2. ETHOSUXIMIDE

Ethosuximide ((2-ethyl-2-methyl-succinamide) has been used by clinicians to treat CAE ever since its anticonvulsant properties were first studied in mouse models in the 1950s [4]. It is generally the choice of drug to suppress absence seizures whereby generalized tonic-clonic seizures or focal onset seizures do not coexist, for the control of these seizures differs from ETX's mechanism of action and hence lies beyond its clinical spectrum [2][5]. The exact action mechanism of ETX has yet to be elucidated. However, existing data suggest that the drug acts to block transient, low-threshold calcium currents generated by T-type calcium channels located in the thalamus, which induce synchronized activation of spike-wave discharges that are responsible for absence seizures [2][4].

To treat CAE, the optimal starting dosage is 10-15 mg/kg/day, which then gradually increases with upward titrations until the target dosage is achieved and well maintained [5]. When ingested orally, ETX has nearly perfect bioavailability and is rapidly absorbed in the gastrointestinal tract. However, this characteristic of the drug makes gastrointestinal disturbances by far the most frequently reported side effects among patients on ETX [2][6]. While these adverse effects are completely reversible and often diminish after the first one to two weeks of treatment, the discomfort may contribute partly to drug discontinuation. Abdominal pain, vomiting, diarrhea, and hiccups are among the most common ones and can be effectively improved by taking the medication along with meals or a switch from liquid to the capsule form [2][4][6]. Drowsiness, lethargy, and sleeplessness are prevalent neurologic adverse reactions induced by ETX. Headaches are the most prevalent type, affecting 14% of children on ethosuximide [2][4]. Only in rare cases, behavior changes that are of clinical significance may occur, including anxiety, depression, and although hardly ever, psychotic symptoms [2]. Specific cognitive problems correlate with increased chances of academic difficulties that could potentially lead to underachievement at school followed by psychosocial consequences. Thus, when choosing a treatment from a list of equally effective drugs for children, cognitive side effects are an important factor to take into consideration [3]. Glauser et al's 2010 study reported that ethosuximide had fewer attentional adverse effects than valproic acid while both drugs appeared more effective in reducing absence seizures than lamotrigine [6].

Idiosyncratic responses associated with ETX such as Stevens-Johnson Syndrome, aplastic anemia, drug-induced lupus, and allergic rashes have been previously reported. Despite a relatively long recovery period, these symptoms usually resolve following medication withdrawal and discontinuation [2][4]. There are no specific guidelines for monitoring ETX treatment, nor are regular laboratory tests such as those for complete blood counts and liver functions required. In-person follow-up appointments are the simplest way to address needs for dosage adjustments, additional tests, or determining the need for drug discontinuation [2][4]. Overall, ethosuximide is considered the optimal initial monotherapy for treating childhood absence seizures in terms of efficacy, tolerability and has a lower rate of unfavorable side effects (26-46%) when compared to other AEDs [4][7].

3. VALPROIC ACID

Valproic acid (VPA) has been generally preferred as the first-line treatment for CAE treatment as a consistent and safe choice of drug that effectively reduces excessive neuronal activity. VPA formulations come in a variety of forms, such as syrup, sprinkle capsules, and tablets. The recommended starting dose of VPA for CAE is 20–30 mg/kg daily divided into two doses. However, this can be raised to 60 mg/kg per day as needed [2]. An ideal titration schedule may involve weekly increments from 10 mg/kg/day to 15 mg/kg/day to 20–25 mg/kg/day. However, thrombocytopenia, a condition characterized by a low level of platelets, is a dose-dependent side effect to be heeded during the administration of VPA. In cases where a patient's platelet count falls below 100,000, additional increases in VPA will be cut off to avoid further complications [2].

VPA acts on a broad spectrum to exert its anti-epileptic effects, of which the most crucial mechanism is its facilitation of the production and release of aminobutyric acid (GABA). As a major inhibitory neurotransmitter in the brain, regulation of GABA-nergic transmission in certain brain areas has a prominent role in controlling the frequency and magnitude of epileptic seizures. Moreover, VPA also has an inhibiting effect on the release of chemicals that are excitatory in nature, further reducing neuronal excitement in the brain. Additionally, VPA blocks voltage-gated ion channels, including sodium, potassium, and calcium channels, as a means to directly mitigate hyperactive neuronal firing [8][9]. Excitingly, preclinical and clinical trials have recently discovered the drug's efficacy in treating psychiatric disorders on account of its modulatory effects on dopaminergic as well as serotonergic transmission [9].

It enhances dopamine release in prefrontal regions of the brain through the upregulation of 5-HT1A receptors. In addition, activation of 5-HT1A combined with downregulation of monoamine oxidases type A (MAO-A) has been associated with VPA's antidepressant effect in animal models [9][10]. This is a promising finding because it makes VPA a more ideal AED option for preemptive measures in the prediction of psychological comorbidity in affected children.

While VPA certainly has its place in epilepsy, its setbacks do not go unnoticed. In particular, the trial conducted in 2010 by Glauser et al. reported that the drug impacts patients' attention to a greater degree than other tested drugs [6]. This stresses again that persistent attention issues and cognitive impairment are essential features of epilepsy and should be addressed with promptness and caution when selecting an antiepileptic medication. Nevertheless, in comparison to older and more recently developed AEDs, adverse effects involving the central nervous system are rather rare among patients on VPA, although a tremor may be present [2][9]. The drug's negative impact on cognitive functions is uncommon and neither is it generally linked to loss of attention or inability to focus caused by fatigability [9]. However, long-term VPA treatment has been found to imply certain harmful effects on neuronal homeostasis and plasticity whereas other studies have identified VPA as a risk factor for Autism Spectrum Disorder and cognitive deficit in children, particularly in cases of in utero exposure [9][11][12]. Based on the findings of retrospective and prospective research, VPA usage has been continuously limited up to date. The findings reported by existing research, combined with further clinical evidence, will aid in determining the true magnitude of VPA's impact across different stages of the neurodevelopment of affected children.

Moreover, nausea, increased appetite, and behavioral/psychiatric changes are among the most commonly reported side effects of VPA. Pancreatitis and hepatic failure, while being rarer, may occur in certain cases: hepatotoxicity affects about one out of every twenty thousand VPA patients and commonly develops within the first 6 months of therapy [5][9]. The condition, however, is obviously age-dependent. Children under the age of two are at significantly higher risk, especially if their seizure disorders are severe or they suffer from neurological conditions, cognitive impairments, or other damage to the brain [9]. Hepatotoxicity commonly develops within the first six months of starting VPA medication. Sargazi et al. (2021) also address valproic acid's tendency to react with patient allergies and metabolic conditions. Potential adverse responses of the metabolic and endocrine systems include vitamin D deficiency, reduced bone mineral density, and hypothyroidism [2][13].

The aforementioned adverse effects could be dose-dependent or idiosyncratic. Hence, tests for blood count and liver transaminases are recommended before treatment and intermittently throughout treatment.

4. LAMOTRIGINE

Lamotrigine (LTG) is another anti-seizure medicine widely used for the treatment of absence epilepsy. Multiple trials have reported seizure freedom ranging from 50% to 80% in CAE patients whereby LTG was used as the first-line monotherapy [2]. However, this has somehow ceased to be the case, for Glauser et al.'s double-blinded, randomized CAE trial in 2010 reported a lower seizure freedom rate after 12 months and a higher frequency of discontinuation due to lack of efficacy in patients treated with LTG than in those treated with ethosuximide or valproic acid [5][6]. In addition to the blockage of voltage-dependent sodium channels, the drug also reduces seizure-inducing misfiring by inhibiting the major excitatory neurotransmitters in the brain, particularly glutamate and aspartate [5]. For a child not taking other antiepileptic medications, LTG is typically administered at 0.6 mg/kg/day as the initial dosage for the first two weeks, 0.6 mg/kg/day increments are then added weekly or biweekly until the target dosage of 5-12 mg/kg/day is reached and well maintained. LTG is available in a variety of dosage forms, including 2-mg, 5-mg, and 25-mg chewable tablets. The drug is easily absorbed and has almost 100% bioavailability when given as oral formulations [2].

Although the various dosages allow for relatively easy titration even in children that are very young, it is still a key limitation of LTG when it is chosen as the first- or second-line therapy. A patient may be at risk of a rare life-threatening condition known as Stevens-Johnson Syndrome (SJS) if the initial dosage was not previously determined or if slow titration was not enforced [7]. Hence, initial titration and maintenance of LTG demand cautious consideration with regard to a titration schedule that expands over multiple weeks and the potential development of SJS rash which affects the skin and mucous membranes [2]. Ataxia, skin rash, and drowsiness have been reported as dose-dependent adverse effects of LTG which are common among all sodium-blocking agents [5]. Glauser et al. 's study reported that LTG has a less negative impact on attention and cognitive functioning in comparison to ethosuximide and VPA [6]. Therefore, LTG remains an excellent choice as a second therapy in cases where a patient does not respond to ETX or has allergic reactions to VPA.

5. ASSOCIATION OF MULTIPLE AEDS

In the case of a diagnosed CAE whereby two monotherapies have failed to control the epileptic seizures, particularly if ethosuximide has been selected as

a first-line or second-line agent, a clinician may resort to combining two or more AEDs to prevent worsening of the symptoms [2]. The association of ETX and VPA has shown promise as the latter reduces the clearance of the former. However, one caveat is that ETX is vulnerable to the effects of other antiepileptic drugs that induce or inhibit enzymes. Co-administration of VPA, which is an enzyme inhibitor, could result in increased serum and brain ETX levels, although the two drugs' additive antiepileptic efficacy may outweigh any consequential neurotoxicity [2][5]. Combining valproic acid and lamotrigine has also proven to be highly efficacious across the globe. The association of VPA and LTG, when titrated with caution, could be especially helpful in tackling CAE forms that are resistant to monotherapies. From the perspective of pharmacodynamic interactions, these two medications are deemed synergistic, meaning they may render significantly more satisfactory outcomes when administered together than when prescribed individually [2]. As VPA actions inhibit LTG metabolism, a patient who has already been on VPA is able to start LTG at a lower dosage, follow a subtler titration schedule, and eventually achieve a lower LTG target dose than when starting without VPA [2]. Furthermore, in refractory CAE cases, genetic screening may be suggested on the ground that absence seizures are suspected to be almost entirely hereditary. While genetic analysis and testing are still a heated debate, examining the specific interactions between each genetic mutation and the mechanism through which they converge to present a similar phenotype could shed light on the disease process and aid health practitioners in devising treatment plans accordingly [5].

6. DISCUSSION

CAE is the most common type of pediatric epilepsy, accounting for 10 to 17 percent of all childhood epilepsy cases [6]. A number of double-blind, randomized experimental trials have been conducted in the field of pediatric epilepsy over the decades. The results of these trials were successful in informing not only ideal initial empirical treatment and strategies but also shed light on a variety of interactive factors that contribute to varying responses and adverse reactions to treatment [2]. Based on Glauser et al.'s study, ETX and VPA had substantially greater efficacy in suppressing epileptic seizures and lower rates of producing intolerable side effects in comparison to lamotrigine [6]. Of the two, ethosuximide affected attention-related cognitive measures to a significantly lesser degree than VPA. In diagnoses of CAE whereby comorbidities of generalized tonic-clonic seizures and focal onset seizures are absent, ethosuximide remains the optimal AED of choice. In cases of treatment failure or resistant forms of the syndrome, it is followed by VPA [2][5].

7. CONCLUSION

Childhood absence epilepsy is defined by daily episodes of brief 10-15 seconds of lapse in consciousness and attention, typically characterized by a fixed stare and blanking of the eyes, bearing a resemblance to daydreaming. Ethosuximide, valproic acid, and lamotrigine are the three primary first-line agents for treating CAE, though unambiguous evidence regarding each medication's clinical profile and drug interaction in polytherapy is lacking. Due to CAE's relatively high remission rates - the majority of patients achieve seizure freedom on the first or second AED - there exist prevalent misunderstandings that the disorder is a benign form of epilepsy. As a result, studies that address the neuropsychiatric and cognitive implications of children on AEDs and the fact that patients remain susceptible to long-term psychosocial challenges over their lifetime. The importance of close monitoring of cognitive, behavioral, and psychological abnormalities during treatment selection as well as long-term follow-up is not adequately advocated for or facilitated. The limitation of this paper is that it is based on previous research and literature. Future research should focus on gathering more clinical evidence on the long-term cognitive, behavioral, and neuropsychological effects of first- and second-line CAE medications. More in-depth investigations are critical to revolutionizing treatment options and improving the quality of life affected children during critical developmental stages.

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