Role of Antiepileptic Drugs in Cognitive and Behavioral Disorders in Patients with Autism Spectrum Disorders

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Abstract

Autism spectrum disorders (ASDs) are a group of syndromes of diverse etiology with a common set of core symptoms that include three core symptoms: communication difficulties, social challenges and repetitive behavior. Drugs for treating these symptoms represent a huge area of unmet need, especially in pediatric population. Side effects affecting lipids and glucose metabolism and neurological status are among main concernes. Newer Antiepileptic drugs (AEDs) have improved side effect profiles and have shown some efficacy in subiects for treating aggressive symptoms in children with ASDs. In this review we examine and illustrate the mechanisms of action of AEDs; we speculate on the possible effect of new AEDs on pathophysiological mechanisms and on their clinical efficacy in cognitive and behavioral disorders of ASDs patients.

Keywords: Autism; Epilepsya; Treatment; Cognition

Abbreviations: ASDs: Autism Spectrum Disorders; AEDs: Antiepileptic Drugs; GABA: Gamma Aminobutyric Acid; NMDA: N-Methyl-D-Aspartate; DBPC: Double-Blind, placebo-Controlled; VPA: Valproate; PBO: Placebo

Introduction

Antiepileptic drugs (AEDs) represent a class of drugs with different pharmacology and chemistry sharing the common ability to decrease neuronal excitability; AEDs are mainly used to treat epilepsy, however, some of them can be used for the treatment of neurological (i.e. migraine, neuropathic pain, hyperkinetic movements disorders) and psychiatric disease (i.e. anxiety bipolar disease, schizophrenia) [1-8] Autism spectrum disorders (ASDs) are a group of syndromes of diverse etiology with a common set of core symptoms that include compromised social interaction, impaired communication, and repetitive behaviors [9,10]. ASDs can be idiopathic or co-morbid with other syndromes such as Fragile X or Rett syndrome. Notwithstanding the wide variation in the etiology, the consistency in

symptomatology suggests that the mechanisms underlying the pathology of ASDs are common. Growing evidence indicates that a possible mechanism could be impairment in the neuronal excitatory/inhibitory balance [10], as suggested by the high prevalence of epilepsy in patients with ASDs [11].

Although the atypical antipsychotics are very effective and commonly used in the treatment of pediatric aggression, there is concern about their prescription in the pediatric patients due to the incidence of side effects such as: metabolic abnormalities, diabetes mellitus, gain weight, insulin resistance, hyperlipidemia, neuroleptic malignant syndrome, dystonias and other extra-pyramidal reactions, including possible tardive dyskinesia [12,13].

Newer AEDs have improved side effect profiles and have shown some efficacy in subiects for treating aggressive symptoms. AEDs may represent a more tolerable long-term treatment for behavioral disorders in ASDs [13,14]. In addition, despite the efficacy of atypical anti-psychotics, there are patients who do not respond to monotherapy. A possible augmentation strategy can include combined treatment with an AED. The purpose of the present review is to relate the mechanisms of action of AEDs to pathophysiological mechanisms and clinical efficacy in cognitive and behavioral disorders in ASDs patients.

Mechanisms of action of Antiepileptic drugs

They can be classified into conventional and newer AEDs [7]. The first group encloses among others: acetazolamide, benzodiazepines, carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone and valproate, while the second comprises: eslicarbazepine acetate, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, retigabine, tiagabine, topiramate, vigabatrin and zonisamide [5,7,15]. Although some AEDs act via more than one single mechanism of action (Table 1), they can also be classified according to the latter into three principal groups:

1) blockers of voltage-dependent sodium channels, so they reduce high-frequency repetitive firing in neurons (carbamazepine, oxcarbazepine, gabapentin, lamotrigine, phenobarbital, phenytoin, topiramate, and valproate);
2) enhancers of GABA-mediated events (via the interaction with specific binding sites on the GABA-A receptor complex, the inhibition of GABA metabolism or the reduction of its neuronal uptake): benzodiazepine, gabapentin, phenobarbital, tiagabine, topiramate, vigabatrin, valproate;
3) Blockers of voltage-gated calcium channels: ethosuximide and zonisamide [2,5,7].

An additional category of AEDs should also be considered according to new and specific mechanisms of action, such a category should comprise: drugs acting directly on excitatory glutamate neurotransmission blocking ionotropic glutamate NMDA (felbamate) and AMPA/kainate (phenobarbital, topiramate, perampanel) receptors [2,5,7]; levetiracetam which binds to synaptic vesicle protein 2A also inhibiting calcium release from intra-neuronal stores, opposing the activity of negative modulators of GABA- and glycine-gated currents, inhibiting excessive synchronized activity between neurons and inhibiting N-type calcium channels [7,16]; retigabine acting as a positive allosteric modulator of KCNQ2-5 (K(v) 7.2–7.5) ion channels [17]. Although the exact mechanisms of action of AEDs might not be considered completely clarified and the fact that newer AEDs do not seem to have an increased efficacy against drug refractory seizures, their use is supported by their overall better safety profile in comparison to traditional agents [7,18]. It has been reported that the new agents possess a better pharmacokinetic profile with a lower liver metabolism, fewer drug interac- tions and/or adverse effects, i.e. cognitive impairment, hepatotoxicity, biochemical as well as hematological alterations [5,19]. Current knowledge indicates that most of AEDs have more than one mechanism of action, contributing to their therapeutic efficacy and tolerability profile [7].

Clinical Use of AEDs in Cognitive and Behavioral Disorders in ASDs Patients

Conventional AEDs

Previous clicinal studies reported that some conventional antiepileptic drugs are effectiviness in the treatment of behavioral and cognitive function in autism spectrum disorder (ASD). They are: valproate, carbamazepine and ethosuximide (Figure 1). Clinical studies reported effects of some AEDs in the behavioral and cognitive function for autism spectrum disorder (ASD). In randomized, prospective, double-blind, placebo-controlled (DBPC) studies, valproate monotherapy reduced repetitive behaviors [20] and irritability [21,22] in individuals with ASD. In a prospective double-blind, placebo-controlled study, 30 subjects (6-20 years of age) with pervasive developmental disorders and significant

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aggression were randomized and received treatment with valproate (VPA) or placebo (PBO) for 8 weeks as outpatients. Mean VPA trough blood levels were 77.8 mcg/mL at week 8. Improvements in irritability, aggression, or general clinical status were not different between the valproate treated and placebo groups [23]. These results may be due by the fact that the majority of the children had a significant intellectual impairment; children were excluded if they had a previous positive response to valproate, and children were tapered off all other psychotropic and anti-epileptic medication just prior to entering the trial. Valproate has also been reported to improve behavioral and core ASD symptoms in a case series of ASD children with and without epilepsy [24] and to substantially improve ASD symptoms in case reports and series of children with subclinical epileptic-like discharges on EEG [13]. In a case series of children with ASD or ASD-like symptoms and epilepsy, Gilbert reported that 41% treated with valproate demonstrated positive psychotropic effects [25]. In a children with Landau-Kleffner Syndrome valproate a improvement in problematic behaviors, and language and social skills [26].

In a case series of children with ASD or ASD-like symptoms and epilepsy, Gilbert reported that 56% treated with carbamazepine demonstrated positive psychotropic effects, even if the evidence is limited to a single case-series [25]. In a retro-spective case-control survey study parents to be one of four AEDs that had the least detrimental effect on behavioral and cognition rated ethosuximide but there was no ratings of improvements in cognitive or behavioral symptoms [27].

In a case series of 66 children with epilepsy, 50 with ASD, and 16 with ASD-like symptoms, Gilbert reported a high prevalence of extremely negative behavioral adverse effects for clonazepam, phenytoin, phenobarbital, and nitrazepam [25] (Figure 1). Given that phenytoin, clonazepam, and phenobarbital were in the group of AEDs rated as having detrimental behavioral and cogni- tive effects on children with ASD in a retrospective case-control survey study [27]. These studies provide good evidence that valproate can have beneficial cognitive and behavioral effects in individual with ASD, while the others conventional AEDs reporting no significant improvements of these functions.
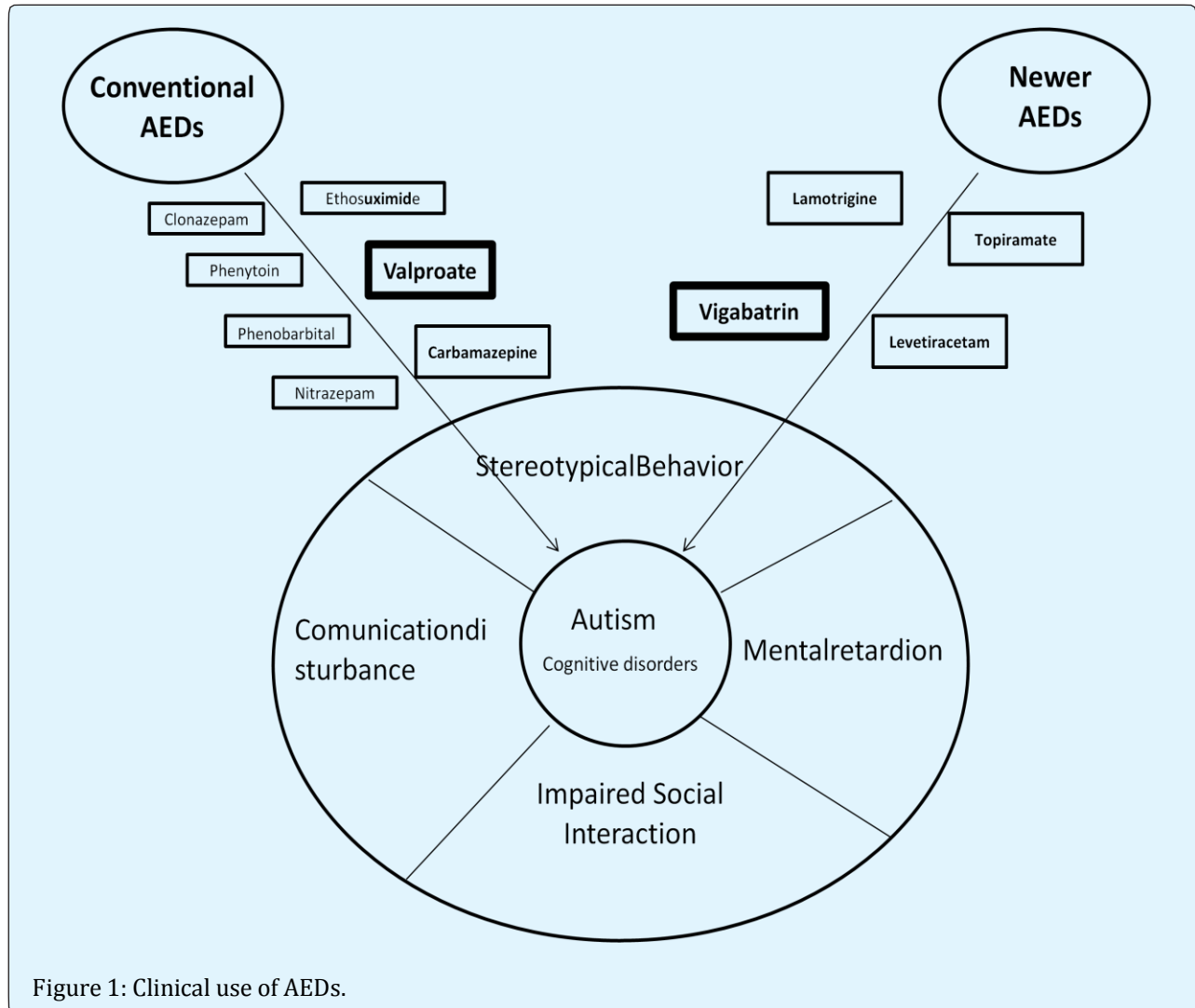
Newer AEDs

In a prospective, open-label trial levetiracetam improved attention, hyperactivity, emotional lability, and aggressive behaviors in six drug-naive boys but not in four boys who had been recently weaned off psychotropic medications [28] However, no significant improvement or worsening of aberrant or repetitive behaviors or impulsivity or hyperactivity was found in a small prospective, randomized, DBPC trial of levetiracetam [29]. Thus, there is insufficient evidence to suggest that levetiracetam improves behavioral or cognitive features of ASD; however, these studies suggest that levetiracetam is well tolerated without detrimental cognitive or behavioral effects.

Lamotrigine did not improve or worsen aberrant or ASD behaviors in a small prospective, randomized, DBPC study [30] but in a case series (Level 4) of 50 children, 28% with ASD, parents reported improvements with lamotrigine in cognitive and ASD symptoms in 62% of children with ASD who had intractable epilepsy, even if seizure frequency did not improve [31]. Although lamotrigine may be cognitively enhancing in non-ASD epileptic individuals [32] and is efficacious for mood stabilization in bipolar disorder [33], there is insufficient evidence to suggest that it improves behavioral or cognitive features of ASD; rather these studies suggest that lamotrigine has few detri- mental cognitive or behavioral effects in individuals with ASD.

In individuals with ASD, topiramate, when added on to risperidone, reduced irritability, stereotypical behavior, and hyperactivity in a DBPC study [34] but caused behavioral adverse effects in some participants in an open-label study [35]. Given the inconsistent results and the fact that topi- ramate can have neurocognitive adverse effects in individuals with epilepsy [36]. These studies regarding the use of newer AEDs showed that have not significant effets in the improvements of behavioral and cognitive functions. Also these studies suggest that levetiracetam is well tolerated without detrimental cognitive or behavioral effects, while lamotrigine has few detrimental cognitive or behavioral effects in individuals with ASD respect to topiramate (Figure 1).

In a clinical study the use of vigabatrin improved cognitive function in children with infantile spasms and with associated epilepsy and autism [37]. Also a improvemet of cognitive function in children affected by tuberous sclerosis were observed [38] So the use of vigabatrin can improvemets the cognitive function in patients with ASD (Figure 1).

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Figure 1: Clinical use of AEDs.

Conclusion and Directions for Future Research

The primary indication for AEDs remains certainly epilepsy, even if other neurological conditions may be treated with these drugs when the typical treatments are ineffective. Several pathophysiological mechanisms inducing a neuronal excitability seems to be involved in an imbalance of both GABAergic and glutamatergic neurotransmissions and therefore could be similar in epilepsy and in cognitive and behavioral disorders ASDs. The main targets for the action of the

AEDs include enhancement of GABAergic inhibition, decreased glutamatergic excitation, modulation of voltage-gated sodium. In the treatment of cognitive and behavioral disorders in ASDs patients there is the potential to use pharmacological agents with GABA-potentiating properties, and studies from animal models of ASDs indicate that a dysfunction in GABAergic signaling within particular neuronal circuits may account for most of the clinical symptoms found in autistic patients. In effect, post-mortem analysis on brain tissues from ASD patients as well as genetic and *in vivo* studies have largely contributed to unveil the impact of GABAergic signaling in these disorders [39]. GABA is involved in different cerebral processes [39]. At the beginning, GABA works as a trophic factor, modulating neuronal migration and maturation [40]. At later developmental stages, when synapses are formed, the release of GABA and glutamate, generate a primitive form of network-driven oscillatory events known as giant depolarizing potentials. γ-Aminobutyric acid is released from GABAergic cerebral

interneurons. GABAergic interneurons not only exert a powerful control on network excitability but, in spite of their relatively low number (10–15% of the entire neuronal population), are able to synchro- nize a large number of principal cells giving rise to coherent oscil-lations, which support different behavioral states of the animals and high cognitive tasks [41]. These observations point to GABA as one of the major players in the early assembly and formation of neuronal circuits in the developing brain. Therefore, it is not surprising that dysfunctions of GABAergic circuits have been implicated in various neuro-developmental and psychiatric disorders such as autism.

Several studies have shown that AEDs that acting on GABAergic synapses are able to ameliorate rescue behavioral deficits and to at least some of the symptoms observed in ASDs patients. Valproate that prevents degeneration and induces a regeneration of GABAergic interneurons [42] is effective in the improvement of cognitive and behavioral effects in individual with ASD. Also a treatment with vigabatrin, which blocks GABA catabolism by inhibiting GABA transaminase, is able to to improve the autistic behavior of children affected by tuberous sclerosis [43]. AEDs with effects on decreasing glutamatergic neurotransmission on and/or voltage sodium or calcium channels may be also advantageous in non-epileptic conditions in ASDs patients. Clinical observation, however, suggests that compared with conventional AEDs, the newer AEDs are more tolerated and have less pharmacodynamic interactions [39, 5].

Research supporting the effectiveness of AEDs in cognitive and behavioral management in patients with ASDs is still inadequate and the limitations of existing research constitute substantial challenges in developing AED therapy recommendations for these disorders. So, more prospective clinical trials are necessary to confirm the efficacy of both conven- tional and newer AEDs in cognitive and behavioral disorderd in ASDs and determine better the proportion of responders in a larger group of patients.

In the future, a better understanding of the AEDs mechanisms of actions in cognitive and behavioral disorders in ASDs patients should be provided by increased knowledge of the underlying molecular deficits in these Fuctions in patients with AEDs disorders.

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