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Review article

Cognitive and behavioral effects of new antiepileptic drugs in pediatric epilepsy

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Abstract

Background: In pediatric epilepsy, neurodevelopmental comorbidities could be sometimes even more disabling than seizures themselves, therefore it is crucial for the clinicians to understand how to benefit these children, and to choose the proper antiepileptic drug for the treatment of epilepsy associated to a specific neurodevelopmental disorder. Aim of this paper is to discuss the potential impact on cognition and behavior of new and newest AEDs and to guide the choice of the clinicians for a targeted use in epilepsy associated with specific neurodevelopmental disorders.

Methods: Information in this review is mainly based on peer-reviewed medical publications from 2002 until October 2016 (PubMed). We choose to include in our review only the AEDs of second and third generation approved for pediatric population.

Results: Vigabatrin, lamotrigine, topiramate, levetiracetam, oxcarbazepine, zonisamide, rufinamide, lacosamide, eslicarbazepine, and perampanel have been included in this review. The most tolerated AEDs from a cognitive and behavioral point of view are lamotrigine and rufinamide, thus representing optimal drugs for children with cognitive and/or attention problems.

Discussion: Most of the new AEDs are initially licensed for adult patients. Data on children are usually very limited, both in terms of efficacy and safety, and the use standardized cognitive and behavioral outcome measures are very limited in pediatric clinical trials.

Conclusion: Several factors including polytherapy, administration of AEDs with the same mechanism of action and the dose and titration of the drug, should be considered as important in the development of cognitive and behavioral side effects.

Keywords: Epilepsy; Children; Antiepileptic drugs; Cognition; Behavior

1. Introduction

In pediatric epilepsy, neurodevelopmental comorbidities could be sometimes even more disabling than seizures themselves, therefore it is crucial for the clinicians to understand how to benefit these children, and to choose the proper antiepileptic drug (AED) for the treatment of epilepsy associated to a specific neurodevelopmental disorder. Therefore, the primary goal of this choice should be not only to reduce seizures, but also to avoid the worsening of the neuropsychological and cognitive problems already present, and a secondary aim should be trying to improve them, if possible.

Intellectual disability (ID), Autism Spectrum Disorders (ASDs) and Attention Deficit Hyperactivity Disorder (ADHD) are the most commonly reported

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neurodevelopmental disorders associated with pediatric epilepsy with possible self-injury and aggression, and need careful evaluation since some AEDs can increase these behaviors [1,2]. ID is the most common comorbidity. The co-occurrence of ASDs and ADHD in pediatric epilepsy has a widely variable prevalence, depending on sampling methods, population studied, age and methods used to diagnose epilepsy and ASD and ADHD [3–5].

During the past few years, new AEDs with novel mechanisms of action have been introduced, generally showing lower rate of side effects, reduced need for serum monitoring, and fewer drug-to-drug interactions, without significant differences in effectiveness [6].

Aim of this paper is to discuss the potential impact on cognition and behavior of new and newest AEDs and to guide the choice of the clinicians for a targeted use in epilepsy associated with specific neurodevelopmental disorders.

2. Search strategy

Information in this review is mainly based on peer-reviewed medical publications from 2002 until October 2016 (PubMed). Few significant historical references have also been considered. Search terms included "pediatric epilepsy", "antiepileptic drugs and cognition", "antiepileptic drugs and behavior", and "antiepileptic drugs and mood". We choose to include in our review only the AEDs of second and third generation approved for pediatric population. Only articles published in English were reviewed. All articles were read by the authors, and references were reviewed to identify any additional relevant studies.

3. Vigabatrin

Vigabatrin (VGB) is a structural analogue of gamma aminobutyric acid (GABA), irreversibly inhibiting the enzyme GABA transaminase. Severe abnormal behaviors following VGB administration affect about 6% of treated children, maybe related to dosage and speed of introduction [7]. As the use of this AED is mostly limited to young patients with very severe forms of epilepsy, few studies have been carried out to specifically investigate the cognitive side effects of VGB, however some data are available on the long-term follow-up of treated children. An important finding concerns the fact that the shorter the period from tuberous sclerosis related infantile spasms onset to seizure control with VGB, the better the long-term cognitive outcome will be [8,9].

4. Lamotrigine

Lamotrigine (LTG) is recommended as monotherapy for the first-line treatment of newly diagnosed focal seizures and as adjunctive therapy of refractory focal seizures in children, as well as second-line monotherapy drug for new-onset generalized seizures and as adjunctive treatment of refractory generalized seizures [10]. LTG has an indirect antiglutamatergic effect by blocking voltage-gated sodium channels and stabilizing neuronal membranes and glutamate release; it also modulates calcium and potassium conductance with a general inhibitory effect on neuronal excitability [11].

LTG has beneficial effect on behavioral problems, such as aggression and impulsivity, and it is indicated to stabilize mood in adolescents with bipolar disease, having an acute and prophylactic antidepressant activity, probably reducing cortical excitability in important regions for the pathogenesis of mood disorder [12,13]. However, LTG might induce behavioral problems in patients with epilepsy and ID, probably due to increased alertness and self-assertion secondary to effective treatments with a low sedative potential [14].

In children and adolescents LTG didn't show clinically significant cognitive effect, although some improvement in concentration and vigilance was reported [15,16]. The cognitive and behavioral long-term effects of LTG and controlled-release CBZ have been compared, revealing that LTG-treated patients showed a better performance on phonemic verbal fluency and selective attention; in contrast, the CBZ group showed more positive behavioral effects than the LTG group [17].

5. Topiramate

Topiramate (TPM) is a broad-spectrum AED that potentiates GABAergic neurotransmission, inhibits voltage-gated sodium and calcium channels, AMPA-type glutamate receptors and carbonic anhydrase. It usually induces weight-loss, thus finding an application in children and adolescents with epilepsy and comorbid obesity and/or binge-eating disorder [18].

A high percentage of children and adolescents (>20%) suffer from a broad range of cognitive side-effects. TPM has been associated to cognitive dysfunction, which can be identified by neuropsychological tests even in those individuals not reporting cognitive decline [19]. Various domains of cognition are affected by TPM, including attention, memory, processing speed, verbal fluency function, and word-finding difficulties [19]. Moreover, other studies analyzed verbal processing tests identifying a negative effect of TPM while LTG and gabapentin showed a significantly smaller effect [19]. Neurophysiologic and functional neuroimaging studies demonstrated that TPM was associated with working memory impairment and with an under-activation of the whole brain, markedly in the language network [20]. In a randomized, double-blind, placebo-controlled study comparing different dosages of TPM (50 and 100 mg/day) and placebo, the TPM 100 mg/day dose