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TOLERABILITY OF ANTI-EPILEPTIC DRUGS IN CHILDREN

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Abstract:

Introduction: *Many cognitive side effects that affect sleep, attention and recall of information in epileptic children were reported. Because it is a critical age in development of cognitive functions, its vital to know how to choose a safe anti-epileptic treatment.*

Aim: *In this review the literature about cognitive side effects of AEDs was searched to identify drugs which have a significant cognitive side effects in children.*

Methods: *The MEDLINE search was conducted after construction of search strategy. The study should be a clinical trial published in the period 2008-2018 and aimed to identify side effects of AEDs to be eligible in the review. The full texts of the eligible studies were read by to investigators to ensure they were met inclusion criteria. The data about characteristics of the included studies, used AEDs and their side effects were extracted using data extraction tables.*

Results: *The search of the literature resulted in 69 studies and after exclusion of irrelevant, duplicated and review studies, 8 studies found to meet the inclusion criteria. Levetiracetam was investigated in four included studies, while other studied AEDs were perampanel, lacosamide, rufinamide, and topiramate. The most common cognitive side effect reported by the included studies was somnolence, followed by dizziness, nervousness, and aggression.*

Conclusion: *These new anti-epileptic drugs showed good tolerability profile in term of cognitive side effects, particularly lacosamide and perampanel. The age of children is the major determinant of the side effects associated with AEDs.*

Keywords: *Side effects, Epilepsy, Treatment, Neonates.*

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INTRODUCTION:

Epilepsy is the existence of more than one seizure, a disease of the brain that is considered having a permanent tendency to make epileptic seizures which has a cognitive, psychological and neurological impact [1].The prevalence and incidence of epilepsy among children is high in rural areas of developing countries and low in developed countries. Globally, the incidence of children's epilepsy ranges from 41-187/100,000 and the prevalence ranges from 3.2-5.5/1,000 individuals [2].

Since Epilepsy is a neurological disorder that has its impact on the cognitive and behavioral functions of the brain in all patient's groups including children [3]. Not only epilepsy but also antiepileptic drugs (AEDs), although they manage to ease and deal with seizures accompanied this disease, they also have some side effects on children's awareness, attention and recall of information [4,5]. These side effects could be attributed to the use more than one drug in treatment of epilepsy with a relatively high concentration reaching the brain. Due to these variation every case should be treated individually [6,7]. Because it is a critical age in development of cognitive functions, its vital to know how to choose the right kind of drug in a way to reduce the frequency and intensity of seizers. Additionally, it is important to ensure that children can enjoy normal life. The side effect of different epileptic drugs should be assessed and monitored through a well stablished system of adverse drug reactions [8,9]. In this review the literature about cognitive side effects of AEDs was searched to identify drugs which have a significant cognitive side effects in children.

METHODS:

The MEDLINE search was conducted after construction of search strategy "(children OR pediatric OR infants) AND ("antiepileptic drugs" OR "antiepileptic medication") AND (side effects OR adverse effects)". The study should be a clinical trial published in the period 2008-2018 and aimed to identify side effects of AEDs to be eligible in the review. The full texts of the eligible studies were read by to investigators to ensure they were met inclusion criteria. The data about characteristics of the included studies, used AEDs and their side effects were extracted using data extraction tables. The findings of the included studies were presented in table 1.

RESULT:

The search of the literature resulted in 69 studies and after exclusion of irrelevant, duplicated and review studies, 8 studies found to meet the inclusion criteria. Included studies aimed to determine, from the best available evidence, what is the cognitive side effect of the antiepileptic drugs used in children. The number of recruited patients ranged from 6 patients in the prospective pilot study conducted by Furwentsches *et al*. [10] and 284 patients in a study of Ness *et al*. [7]. Regarding the mean age of included children, it ranged from one month old Furwentsches *et al*. [10] to 12.3 years old [11]. Taking into the consideration the epilepsy onset, Levisohn *et al*. [5] reported the onset of epilepsy to be minimally 6 months before the study, Kim *et al*. [12] reported a range of 28.7 - 39.0 months, Grosso *et al*. [11] reported a range of 5.4–12.5. Five include studies did not report the onset age of the epilepsy [3,7,13-15].

Types of epilepsy included partial epilepsy [5,7,15], the Lennox-Gastaut syndrome [12,16], and the refractory epilepsy in a study of Callenbach *et al*. [13]. Furthermore, neonatal seizures was studied by Furwentsches et al. [10]. Meador *et al*. [3] studied perampanel and found 30.6% of children having dizziness and somnolence was detected in 15.3%, while Grosso *et al*. [11] studied lacosamide and found 44% of children suffered dizziness as side effects of the treatment.

Oral levetiracetam is studied in neonates revealing only one of six infants had mild sedation [10], while Callenbach *et al*. [13] investigated levetiracetam as add-on therapy and reported side effects such as hyperactivity, somnolence, irritability, and aggressive behavior in 48.5%, 36.4%, 33.3%, and 27.3% of epileptic children respectively. Levisohn *et al*. [5] investigated levetiracetam and found adverse effects such as headache, fatigue, somnolence, and aggression in 26.6%, 14.1%, 14.1% and 12.5% of epileptic children. Perry *et al*. [15] compared levetiracetam with carbamazepine, the incidence of most reported side effects was higher in carbamazepine including somnolence, dizziness, poor sleep, poor concentration, only behavior/irritability was higher in levetiracetam. Side effects of other ADEs as rufinamide was reported as somnolence, hyperactivity, poor sleep quality [12]. Furthermore, topiramate reported side effects include anorexia, somnolence, nervousness in 35%, 27%, and 13% of epileptic children, respectively [7].

DISCUSSION:

After more than a century of introducing of bromide as the first treatment of epilepsy, the associated side effects remain the main challenge of treatment success in all AEDs [17]. The patients' adherence is affected by these adverse effects which leads to early

discontinuation of anti-epileptic therapy in up to a quarter of patients [18]. Available AEDs can impair the cognitive functions of epileptic patients which affects patients' quality of life. The extent of the cognitive side effects, such as memory impairment and mental deficits, depends on patients' characteristics and treatment related factors [19]. In the last decades, many new AEDs have been investigated with claims that these new drugs have better efficacy and less side effects. However, the AEDs therapy in children can lead to serious cognitive side effects such as attentional deficit disorder, learning abilities, language and verbal difficulties [9]. This review aimed to identify cognitive side effects of AEDs reported in the literature.

Levetiracetam was investigated in four included studies [5,13-15], while other studied AEDs were perampanel [3], lacosamide [16], rufinamide [20], and topiramate [7]. As the mean age of included children increased, the cognitive effects associated with levetiracetam became more obvious. This mainly attributed to ability to report the cognitive effect by the investigators or children as they become older. Furthermore, studies of large sample size [5,7,15,20] seems to report more side effects than studies with small sample size (n<30). It is an effect of statistical power associated with large sample size which can detect significant side effects of AEDs. The most common cognitive side effect reported by the included studies was somnolence [3,5,7,13,15,20], followed by dizziness [3,15,16], nervousness [7,13,15], and aggression [5,13]. The tolerability of levetiracetam was better than that of carbamazepine in children as demonstrated by Perry *et al*. [15]. When levetiracetam compared to placebo in a study of *Levisohn et al*., no significant differences were found between side effects reported in levetiracetam group or those reported in placebo group [5]. The tolerability profile of perampanel found good with only dizziness and somnolence reported in 30% and 15% of 133 children included in the study [3]. Similarly, lacosamide used as add-on therapy and only dizziness was reported as side effect of treatment [16].

CONCLUSION:

These new anti-epileptic drugs showed good tolerability profile in term of cognitive side effects, particularly lacosamide and perampanel. The age of children is the major determinant of the side effects associated with AEDs. As the children become older, the cognitive side effects of AEDs treatment become more detectable.

CONFLICT OF INTERESTS:

As no financial response was received for conduction of this review, no conflict of interests is declared by the authors.

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Table (1): Summary table summarize characteristics of included study and cognitive side effects of anti-epileptic drugs among children

Study	Study design	Sample size	Age of patients	Type of epilepsy	Anti-epileptic drugs	Comparison drugs (if present)	The cognitive side effects
(Meador et al., 2016) [3]	Double blinded RCT	133	12 to <18	Partial-onset seizures	Perampanel	Placebo	No differences between perampanel (n = 79) vs. placebo (n = 44) in System Global Cognition Score. Dizziness (30.6%) Somnolence (15.3%)
(Fürwentsches et al., 2010a) [10]	Pilot study	6	Neonate	Neonatal seizures	Levetiracetam	None	Mild sedation in one infant
(Callenbach et al., 2008) [13]	Prospective multi-centre, open-label, add-on study	33	4-16 years (median 8.5 years)	Refractory epilepsy	Levetiracetam	None	Hyperactivity (48.5%) Somnolence (36.4%) Irritability (33.3%) Aggressive behavior (27.3%)
(Grosso et al., 2014b) [11]	Multicenter, retrospective, open-label clinical study	18	12.3 (mean age) Range from (5.6–15)	Lennox-Gastaut syndrome	Lacosamide as add on therapy	None	Dizziness
(Kim et al., 2012a) [12]	Open-label, observational clinical	128	9.4 ± 4.7 (1.8–	Lennox-Gastaut syndrom	Rufinamide	AEDs	Patients with any adverse effect= 32.8% Somnolence 4.7%

	trial		19.9) years	e			Hyperactivity 4.7% Poor sleep quality 3.9%
(Levisohn et al., 2009) [5]	Randomized, double-blind, placebo-controlled, noninferiority trial	99	4-16 years	Partial-onset seizures	Levetiracetam	Placebo	Adverse events were reported by 89.1% levetiracetam-treated and 85.3% placebo-treated patients. Headache 26.6% Fatigue 14.1% Somnolence 14.1% Aggression 12.5%
(Ness et al., 2012) [7]	Double blinded placebo-controlled trial	284	1 and 24 months	Refractory, partial-onset seizures	Topiramate	Placebo	Adverse effects in 52% of children Anorexia (35%) Somnolence (27%) Nervousness (13%)
(Perry et al., 2008) [15]	Retrospective RCT	86	≤ 16 years of age	Partial epilepsy	Levetiracetam	Carbamazepine	In levetiracetam: Somnolence %9 Dizziness %1.5 Behavior/irritability %30.3 Poor sleep %1.5 Poor concentration %1.5 In carbamazepine: Somnolence(%40) Dizziness(%10) Behavior/irritability(%5) Poor sleep(%10) Poor concentration(%15)