Review Article

ISSN: 2675-3626

Epilepsy in childhood: an update on management

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Background: The aim of this study was to review the current database for the management of childhood epilepsy, presenting and comparing the different types of treatment, focusing on the ones with the best efficacy.

Methods: Original articles related to the subject were obtained from SciELO, PubMed and BVS databases using terms from "Health Sciences Descriptors" and "Medical Subject Headings" (MeSH). Results: Around 70% of individuals with epilepsy can become seizure-free and go into long-term remission after starting the use of AEDs in monotherapy. On the other hand, drug-resistant seizures are treated through a surgical approach, which despite good results, is still underused.

Conclusions: The AEDs are the most used approach nowadays, and for the choice of the best drug, one should take into account the primary and secondary results indicated in this review. The results presented regarding the safety and efficacy of surgical treatment seek to encourage its use.

Keywords: Epilepsy; Disease management; Child; Neurosurgery

INTRODUCTION

Epilepsy is a neurological disease that can be defined as the temporary appearance of signs and symptoms due to abnormal neuronal discharges in the cerebral cortex. The causes can be genetic, head trauma, stroke, brain infection, among others [1]. Approximately 50 million people worldwide have epilepsy, making it one of the most common neurological diseases [2]. Regarding the pediatric population, epilepsy is one of the most common neurological disorders, affecting up to 0.5% of children [3]. During the first ten years of life, one in every 150 children is diagnosed with this syndrome, which predominates in childhood. Still regarding children, although there are signs of a reduction in incidence over the last few decades, the average annual rate of new cases is five to seven cases per 10,000 children, from birth to fifteen years of age [2]. Treatment can be performed using antiepileptic drugs that prevent the abnormal brain electrical discharges that originate epileptic seizures. However, around 20% of the patients have refractory seizures, that is, those that do not respond to antiepileptic drugs, and are therefore susceptible to surgical treatment, such as resective surgeries. There are also stimulations, still little used, of the vagus nerve, cerebellum or thalamus. Whatever the type of treatment, the objective is to control seizures and improve the patient's quality of life. As it is one of the most prevalent neurological diseases in childhood, this study aims to review the current database for the management of childhood epilepsy. This article contains the last and best efficacy evidence in pharmacological and non-pharmacological approaches, such as anti-epileptic drugs (AEDs), surgery and magnetic stimulation, so that physicians can choose the best approach for each patient based on "time for treatment failure", "time to first seizure", among others.

METHODS

This is a systematic review written in 2022 with the purpose to present current database about the management of childhood epilepsy using pharmacological or non-pharmacological approaches. The selection of the articles used the following databases: Virtual Health Library (BVS), PubMed and Scientific Electronic Library Online (SciELO). The search descriptor used were: "epilepsies"; "management"; "child". After reviewing the article, the following MeSH terms were used: "epilepsy"; "disease management"; "child"; "neurosurgery".

Inclusion criteria: systematic review articles available in full, in Portuguese or in English, published from 2017 to 2022 and articles discussing the pharmacological and surgical management of childhood epilepsy. Exclusion criteria:

Received: 19 July 2022
Accepted: 08 January 2023

articles with no relation to the theme and duplicated texts in the databases.

Were identified 9.908 articles, being 1 from SciELO, 5.394 from PubMed and 4.513 from BVS. Of these, 9 articles were excluded due to duplicity, remaining 9.899. After the filters “full text”, “free full text”, “from 2017 to 2022” and “systematic review”, being applied, the number of articles was reduced to 90 (PubMed: 58; BVS: 32). After reading the title and abstract, 62 texts were excluded because the management was not related to pharmacological or surgical measures and because the data were not applied to children. Therefore, 28 articles were evaluated. After the texts were read in full, 4 were excluded for no relation to the theme. Thus, the final sample contained 24 articles and 2 books. After reviewing the article and using the MeSH terms, a new bibliographic search resulted in 1.153 articles, 63 from BVS, 1.090 from PubMed and none from SciELO. Of these, 3 articles were excluded due to duplicity, remaining 1,150. After the filters “full text”, “free full text”, “from 2017 to 2022” and “systematic review”, being applied, the number of articles was reduced to 426 (PubMed: 407; BVS: 19). After reading the title and abstract, 381 texts were excluded because they were not compatible with the article's theme. Therefore, 45 articles were evaluated. After the texts were read in full, 36 were excluded for no relation to the theme. Thus, the remaining 9 references were added to the 24 previously selected references, resulting in 33 articles; the two previously used books were excluded and 2 references from other sources were added, totaling 35 references. The flow diagram of search strategy and study selection is shown on figure 1.

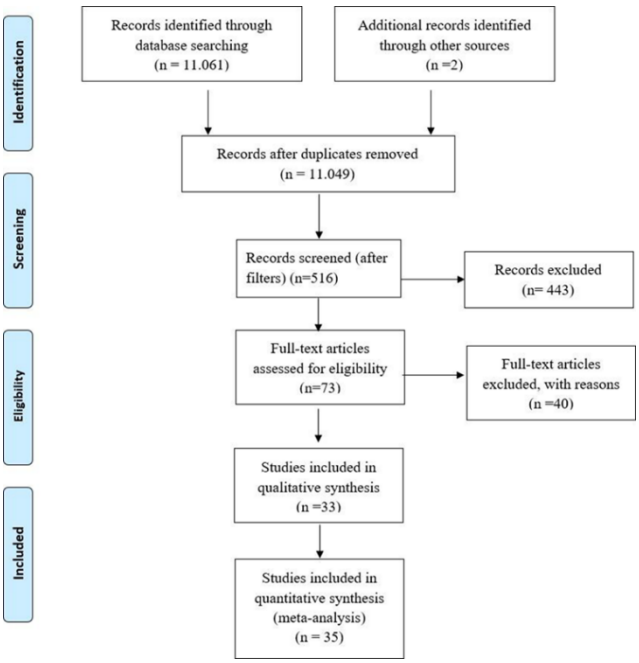

Figure 1- Flowchart of search strategy and study selection.

RESULTS

Pharmacological treatment

With regard to antiepileptic drug monotherapy for epilepsy, 11,865 out of 12,391 participants (96%), 4058 (34%) individuals prematurely withdrew; fewest participants withdrew from levetiracetam (27%) and sodium valproate (28%) and the most participants withdrew from gabapentin (47%) and phenobarbitone (38%). The most commonly reported reason for withdrawal from treatment was due to adverse events (38% of all withdrawal events); fewest participants withdrew from gabapentin (20%) and phenobarbitone (20%) due to adverse events and the most participants withdrew from carbamazepine (45%) and topiramate (48%) due to adverse events. Inadequate response (ie lack of seizure control) was reported as the reason for withdrawal for 27% of participants ranging from 16% of participants on phenobarbitone to 62% of participants on gabapentin. For secondary outcome ''time to first seizure'' for individuals with partial seizures, phenobarbitone performed significantly better than both current first-line treatments carbamazepine and lamotrigine; carbamazepine performed significantly better than sodium valproate, gabapentin and lamotrigine. Phenytoin also performed significantly better than lamotrigine (high-quality evidence). In general, the earliest licensed treatments (phenytoin and phenobarbitone) performed better than the other treatments for both seizure types (moderate- to high-quality evidence) [4].

In a parallel established between phenobarbital and phenytoin as monotherapy for epilepsy, the primary results found were: ''time to treatment failure for any reason related to treatment'' (pooled HR adjusted for seizure type for 499 participants: 1.61, 95% CI 1.22 to 2.12, low-certainty evidence), ''time to treatment failure due to adverse events'' (pooled HR adjusted for seizure type for 499 participants: 1.99, 95% CI 1.37 to 2.87, low-certainty evidence), ''time to treatment failure due to lack of efficacy'' (pooled HR adjusted for seizure type for 499 participants: 1.87, 95% CI 1.32 to 2.66, moderate-certainty evidence), showing a statistically significant advantage for phenytoin compared to phenobarbitone. Finally, there is statistically significant evidence of an interaction between epilepsy type (focal onset versus generalized onset) and treatment effect (test of subgroup differences: P = 0.04, I2 = 76.5%; Analysis 1.4), that is, it appears that the treatment effect of phenytoin may be larger for individuals with generalized onset seizures compared to individuals with focal onset seizures [5].

As for the use of oxcarbamazepine or phenytoin in monotherapy for the treatment of epilepsy, it was found that for “time to treatment failure for any reason related to treatment” there was an advantage of oxcarbazepine over phenytoin, but this was not statistically significant (pooled HR adjusted for epilepsy type: 0.78 95% CI 0.53 to 1.14, 476 participants, two trials, moderate-quality evidence). Analysis showed that “treatment failure due to adverse events” occurred later on with oxcarbazepine than phenytoin (pooled HR for all participants: 0.22 (95% CI 0.10 to 0.51, 480

participants, two trials, high-quality evidence). To "treatment failure due to lack of efficacy", there was no clear difference between the drugs (pooled HR for all participants: 1.17 (95% CI 0.31 to 4.35), 480 participants, two trials, moderate-quality evidence) [6].

When sodium valproate and phenytoin were compared as monotherapy for epilepsy, the following primary results were observed: "time to treatment failure for any reason related to treatment" (pooled HR adjusted for seizure type 0.88, 95% CI 0.61 to 1.27; 5 studies; 528 participants; moderate-quality evidence), "time to treatment failure due to adverse events" (pooled HR adjusted for seizure type 0.77, 95% CI 0.44 to 1.37; 4 studies; 418 participants; moderate-quality evidence), "time to treatment failure due to lack of efficacy" (pooled HR for all participants 1.16 (95% CI 0.71 to 1.89; 5 studies; 451 participants; moderate-quality evidence). These results suggest that "treatment failure for any reason related to treatment" and "treatment failure due to adverse events" may occur earlier on phenytoin compared to sodium valproate, while treatment failure due to lack of efficacy may occur earlier on sodium valproate than phenytoin; however none of these results were statistically significant. Results for "time to first seizure" (pooled HR adjusted for seizure type 1.08, 95% CI 0.88 to 1.33; 5 studies; 639 participants; low-quality evidence) suggest that first seizure may occur slightly earlier on sodium valproate compared to phenytoin [7].

When comparing lamotrigine to carbamazepine, the results "time to treatment failure for any reason related to treatment" (pooled HR adjusted for seizure type: 0.71, 95% CI 0.62 to 0.82, moderate-quality evidence), "time to treatment failure due to adverse events" (pooled HR adjusted for seizure type: 0.55 (95% CI 0.45 to 0.66, moderate-quality evidence) and "time to treatment failure due to lack of efficacy" (pooled HR for all participants: 1.03 (95% CI 0.75 to 1.41), moderate-quality evidence) demonstrated a significant advantage for lamotrigine compared to carbamazepine in terms of "treatment failure for any reason related to treatment" and "treatment failure due to adverse events", but no difference between drugs for "treatment failure due to lack of efficacy". "Time to first seizure" (pooled HR adjusted for seizure type: 1.26, 95% CI 1.12 to 1.41,high-quality evidence) showed a significant advantage for carbamazepine compared to lamotrigine for first seizure and six-month remission [8].

Regarding the use of topiramate or carbamazepine as monotherapy for the treatment of epilepsy, for individuals with focal onset seizures, a statistically significant advantage for carbamazepine was shown for "time to failure for any reason related to treatment" (HR 1.21, 95% CI 1.01 to 1.46), "time to treatment failure due to lack of efficacy" (HR 1.47, 95% CI 1.07 to 2.02), and "time to 12-month remission" (HR 0.82, 95% CI 0.69 to 0.99). There was no statistically significant difference between topiramate and carbamazepine for ''time to first seizure'' and ''time to six-month remission'' [9].

When comparing carbamazepine to phenobarbital as monotherapy for epilepsy, the following primary results were observed: "time to treatment failure for any reason related to treatment" (pooled HR adjusted for seizure type for 676 participants: 0.66, 95% CI 0.50 to 0.86, moderate - quality evidence), "time to treatment failure due to adverse events'' (pooled HR adjusted for seizure type for 619 participants: 0.69, 95% CI 0.49 to 0.97, low-quality evidence), "time to treatment failure due to lack of efficacy" (pooled HR adjusted for seizure type for 487 participants: 0.54, 95% CI 0.38 to 0.78, moderate-quality evidence). Thus, there is a statistically significant advantage for carbamazepine compared to phenobarbitone. With regard to secondary outcomes, no statistically relevant evidence was found between carbamazepine and phenobarbitone, as demonstrated in "time to first seizure post-randomisation" (pooled HR adjusted for seizure type for 822 participants: 1.13, 95% CI 0.93 to 1.38, moderate-quality evidence). There was a statistically significant interaction between treatment and seizure type (test for subgroup differences: P = 0.02 calculated with fixed-effect meta-analysis), i.e., phenobarbitone may have an advantage over carbamazepine for individuals with seizure focals and vice versa for individuals with generalized seizures [10].

Concerning the use of carbamazepine or phenytoin as monotherapy for the treatment of epilepsy, there is some evidence of an advantage for phenytoin for individuals with generalized onset seizures for "time to withdrawal of allocated treatment" primary outcome: pooled HR 0.42 (95% CI 0.18 to 0.96); and a statistical interaction between treatment effect and epilepsy type (partial versus generalized) for this outcome (P = 0.02) was found. Three hundred and eighty-three out of 582 participants (66%) experienced a recurrence of seizures; 192 out of 297 (64%) on phenytoin and 191 out of 285 on carbamazepine (67%). the overall pooled HR (for 582 participants) was 0.88 (95% CI 0.72 to 1.08, P = 0.21), suggesting a slight advantage to phenytoin, which is not statistically significant [11].

About the safety and tolerability of lacosamide (LCM), four randomized clinical trials (RCTs) compared 13 types of adverse effects (AEs) between LCM and placebo. Overall, the total incidence of AEs between the two groups was not significantly different (p = 0.15). When comparing lacosamide to topiramate, the total incidence of AEs between the two groups was not significantly different (p = 0.10). There were significant differences in the incidences of paresthesia [RR = 0.05; 95% CI (0.00, 0.85); p = 0.04], fatigue [RR = 0.02; 95% CI (0.00, 0.40); p = 0.009], irritability [RR = 0.04; 95% CI (0.00, 0.76); p = 0.03], and weight loss [RR = 0.03; 95% CI (0.00, 0.57); p = 0.02]. For these four AEs, the incidence in the LCM group was significantly lower than that in the topiramate group. Two cohort studies compared the

incidence of AEs between lacosamide and zonisamide use; total incidence of AEs was not significantly different between the two groups [RR = 0.67; 95% CI (0.39, 1.15); p = 0.15]. However, as for dizziness, the incidence in the LCM group was significantly higher than that in the zonisamide group. Two cohort studies compared lacosamide and levetiracetam for AEs; total incidence of AEs between the two groups was significantly different [RR = 0.67; 95% CI (0.46, 0.96); p = 0.03]. For AEs involving the nervous system, there were significant differences in the incidence of sedation between the two drugs [RR = 0.21; 95% CI (0.08, 0.55); p = 0.001] [12].

With respect to the management of acute tonic-clonic convulsions including convulsive status epilepticus in children, the efficacy of lorazepam, diazepam and midazolam and their different routes of administration were evaluated. Buccal and intranasal anticonvulsants have been shown to lead to similar rates of seizure cessation as intravenous anticonvulsants, eg intranasal lorazepam appears to be as effective as intravenous lorazepam (RR 0.96, 95% CI 0.82 to 1.13; 1 trial; 141 children; high-quality evidence) and intranasal midazolam was equivalent to intravenous diazepam (RR 0.98, 95% CI 0.91 to 1.06; 2 trials; 122 children; moderate quality evidence). Intramuscular midazolam also showed a similar rate of seizure cessation to intravenous diazepam (RR 0.97, 95% CI 0.87 to 1.09; 2 trials; 105 children; low-quality evidence). For intravenous routes of administration, lorazepam appears to be as effective as diazepam in stopping acute tonic clonic convulsions: RR 1.04, 95% CI 0.94 to 1.16; 3 trials; 414 children; low-quality evidence. In general, intravenously-administered anticonvulsants led to more rapid seizure cessation but this was usually compromised by the time taken to establish intravenous access [13].

With regard to the treatment of children with severe myoclonic epilepsy, two randomized clinical trials (RCTs) evaluated the use of stitipentol (STP) (total of 64 children). A significantly higher proportion of participants had 50% or greater reduction in seizure frequency in the STP group compared with the placebo group (22/33 versus 2/31; RR 10.40, 95% CI 2.64 to 40.87). A significantly higher proportion of participants achieved seizure freedom in the STP group compared with the placebo group (12/33 versus 1/31; RR 7.93, 95% CI 1.52 to 41.21). Investigators found no significant differences in proportions of dropouts from the STP group compared with the placebo group (2/33 versus 8/31; RR 0.24, 95% CI 0.06 to 1.03) [14].

Approximately 30% of people with epilepsy do not respond to treatment with currently available drugs. However, medications such as clobazam, lamotrigine, rufinamide, gabapentin vigabatrin and clonazepam can be used as adjuncts in the treatment of drug-resistant epilepsy. Regarding clobazam, seizure freedom was reported by three of the included studies. Collectively, 27 out of 175 patients were seizure-free during treatment with clobazam (3 RCTs, n = 175, very low-quality evidence). There was a slightly higher incidence of treatment withdrawal associated with receiving clobazam, although the overall incidence was still fairly low (4 RCTs, n = 197, very low quality evidence) [15].

Concerning lamotrigine, the overall risk ratio (RR) for 50% or greater reduction in seizure frequency was 1.80 (95% CI 1.45 to 2.23; 12 trials, moderate-certainty evidence) indicating that lamotrigine was significantly more effective than placebo in reducing seizure frequency. The overall RR for treatment withdrawal (for any reason) was 1.11 (95% CI 0.91 to 1.37; 14 trials; 1806 participants; moderate certainty evidence) [16]. With regard to rufinamide, the overall RR for 50% or greater reduction in seizure frequency was 1.79 (95% CI 1.44 to 2.22; 6 RCTs; moderate-quality evidence) indicating that rufinamide (plus conventional AED) was significantly more effective than placebo (plus conventional AED) in reducing seizure frequency by at least 50%, when added to conventionally used AEDs in people with refractory focal epilepsy. The overall RR for treatment withdrawal (for any reason and due to AED) was 1.83 (95% CI 1.45 to 2.31; 6 RCTs; moderate-quality evidence) showing that rufinamide was significantly more likely to be withdrawn than placebo [17]. About the use of gabapentin, the overall RR for reduction in seizure frequency of 50% or more compared to placebo was 1.89 (95% confidence interval (CI) 1.40 to 2.55; 6 trials, 1206 participants; moderate-quality evidence). The RR for treatment withdrawal compared to placebo was 1.05 (95% CI 0.74 to 1.49; 6 trials, 1206 participants; moderate-quality evidence) [18]. As for vigabatrin, participants treated with this drug may be two to three times more likely to obtain a 50% or greater reduction in seizure frequency compared with those treated with placebo (RR 2.60, 95% CI 1.87 to 3.63; 4 studies; low-certainty evidence). Those treated with vigabatrin may also be three times more likely to have treatment withdrawn although we are uncertain (RR 2.86, 95% CI 1.25 to 6.55; 4 studies; very low-certainty evidence) [19]. Finally, with reference to the use of clonazepam, a single-blinded, randomized, clonazepam-controlled, parallel-group trial of clobazam add-on therapy for resistant epilepsy showed a statistically significant difference in the proportion of participants with a 50% or greater reduction in seizure frequency (RR 2.82, 95% CI 1.39 to 5.72); the proportion of participants achieving total cessation of seizures was 7/34 for clobazam group, and 0/32 for clonazepam group; three of the 36 participants in the clobazam group were discontinued during the test, of whom two were due to side effects and one due to delayed administration of clobazam, and 14/40 participants in the clonazepam group were discontinued, of whom 10 were due to side effects, two due to lack of efficacy and two due to delayed administration of clonazepam [20]. The summary of type of seizure and the best AED for the treatment is represented in Table 1.

Table 1- Summary of type of seizure and the best AED for the treatment.

Seizure	*Best drug*
Simple focal	Carbamazepine (oral: 10-20 mg/kg/day, four or three times a day) Lamotrigine (maintenance dose, oral: 1-10 mg/kg/day, one or two times a day).
Absence seizure	Sodium Valproate (oral: 15 mg/kg/day, two or three times a day, increasing 5-10 mg/kg/day until seizures are controlled).
Drug-resistant focal epilepsy	Gabapentin (3-4 years: 40 mg/kg/day, orally, three times a day; 5-11 years: 20-35 mg/kg/day, orally, three times a day; 12 years or older: 300-600 mg, oral, three times a day)
Generalized seizures	Sodium Valproate (oral: 15 mg/kg/day, two or three times a day, increasing 5-10 mg/kg/day until seizures are controlled)
Tonic-clonic seizures	Diazepam (intravenous: 0.3 mg/kg/dose; rectally: 0.5 mg/kg/dose)

Among the known neurosteroids, Allopregnanolone (ALLO) is the potent and the most thoroughly examined natural endogenous positive GABA-A receptor modulator. In 2017, two cases of adults with super-refractory status epilepticus were reported, in whom the introduction of treatment with ALLO (at doses of 5.6 mg/h for 5 days in the form of 120 h continuous infusion) brought positive results. Ganaxolone (3 alpha-hydroxy-3beta-methyl-5alpha-pregnan-20-one; GNX) belongs to exogenous neurosteroids, and is the 3 betamethylated exogenous analogue of ALLO. A Phase II trial was conducted in 147 refractory adults (100 females and 47 males in the age range of 18-69 years) and the results of the trial were quite encouraging—GNX reduced by 18% mean weekly seizure frequency (vs. enhancement in placebo group). Reply rates were evaluated as a percentage of patients in whom reduction of seizures reached at least 50%. The rates were 26 and 13% in GNX and placebo groups, respectively [21].

Surgical treatment

For epilepsy patients who are refractory to medical therapy, surgical treatment can be an option. Temporal and extratemporal surgery are the most used today, although new techniques such as Laser Interstitial Thermal Therapy (LITT), Vagus Nerve Stimulation (VNS), Deep Brain Stimulation (DBS) and Transcranial Magnetic Stimulation (TMS) are emerging.

Surgical outcomes for temporal lobe epilepsy (TLE) in children are generally favorable, with a recent systematic review showing complete seizure freedom in 76% of patients. Consistent predictors of favorable outcomes include a visible lesion on magnetic resonance imaging (MRI), a lack of secondarily generalized seizures, and a lack of bilateral epileptic activity on electroencephalography (EEG). Other potential predictors include duration of epilepsy, a history of febrile seizures and age at surgery, since children 3 years of age or younger have greater rates of seizure freedom compared to patients 4–17 years of age [22, 23]. Regarding adverse effects, a number of cases are affected by superior quadrantonopia, deficits in verbal learning (left-sided/dominant resection) and visual memory (right-sided/non-dominant resection), infections, hemorrhage, hydrocephalus, hemiparesis, cranial nerve deficits (CNDs), hematomas, psychiatric disorders and others [22, 24]. Retrospective analysis of a multi-institutional surgical registry that included data between 2006 and 2014 revealed a mortality rate for temporal lobe resections of only 1.4%; the major complication rate was 6.5% and the readmission rate was 11% [25].

As for extratemporal lobe epilepsy (ETLE) in children, surgical approaches (excluding hemispherectomy) had a seizure-freedom rate of 56%, which is lower than the seizure-freedom rate following TLE surgery. The same review found short epilepsy duration, lesional etiology, absence of secondary generalization, and ictal EEG location to be predictors of better outcomes. Postoperative neurological deficits are not uncommon, but many of these are either transient in nature or predicted and discussed preoperatively. Deficits largely depend on the location of resection; visual field defects (VFDs) often occur after occipital resection, and hemiparesis may be seen in operations near the precentral gyrus. Surgical complications include various infections, hemorrhage, hygroma, and shunt-dependent hydrocephalus [22]. In turn, lobectomy (OR 0.280, 95% CI 0.117–0.651, p = 0.003) was associated with decreased long-term seizure freedom (41.9%) compared to lesionectomy (75.7%) and hemispherectomy (69.4%), which achieved similar results (respectively OR 2.184, 95% CI 0.938–5.458, p = 0.079, and OR 1.493, 95% CI 0.691–3.299, p = 0.313). years, 63.7% (95% CI 55.4–71.2) at 5 years, and 61.2% (95% CI 52.5–69.3) ≥ 10 years of follow-up [3].

With regard to Laser Interstitial Thermal Therapy (LITT), in a review of the existing adult and pediatric patients with hypothalamus hamartoma literature, 87% of patients with at least 1-year follow-up had gelastic seizure control after the procedure and 60 % of patients with non-gelastic seizures had control. This compares favorably to other forms of treatment such as resection or radiosurgery [26]. In a study with 127 participants, with the overall seizure outcome reported in terms of Engel seizure outcome classes, 57.5% of the patients experienced the complete remission of their seizures. For gelastic seizures, single studies reported far

higher rates of seizure freedom (eg [38]: 93% or 78% of patients with 12-month or less than 12-month follow-up, respectively). For many other patients, a worthwhile reduction of seizure frequency and intensity was qualitatively reported (referring to Engel classes 2–3) while only a minority of patients (6.3%) experienced no relevant effect on seizures at all (Engel class 4) [27]. Furthermore, in another study, two-thirds (61%) of patients with refractory epilepsy were free from seizures or from disabling seizures after LITT and only 24% had postoperative complications. These findings indicated that magnetic resonance imaging (MRI)-guided LITT was an effective and well-tolerated approach to the treatment of drug-resistant epilepsy. Finally, some of tand surgical complications of LITT are: adverse functional effects, wound complications, psychiatric symptoms and others; mild hemiparesis, language dysfunction, wound pain and psychiatric symptoms are complications that can be resolved within six months after the procedure [28].

About Vagus Nerve Stimulation (VNS), a study carried out in a group of 362 patients shows a median reduction of seizures of 25.0 %, 40.9 %, 53.3 %, 60.0 % and 66.2 % respectively at 3, 6, 12, 24 and 36 months after implantation.The corresponding response rates (at least 50 % seizure reduction) were respectively 38.9 %, 46.8 %, 55.8 %, 57.7 %, and 58.8% [29]. Regarding the results of the device in children, one study (n=141; 61% under 12 years old) reported the long-term outcome as a mean reduction rate of 76% 10 years after implantation [30]. In addition to the effects on seizures, in a study with 41 children, during the 39 weeks following the implantation of VNS, an improvement in depression scores (Profile of Mood States - POMS; from 13.06–10.11) and overall mood were found (POMS-TMD; from 41.09–30.63) [29].

Regarding Deep Brain Stimulation (DBS), among the 40 patients who participated in one study, 34 (85%) patients had seizure reduction with the procedure, and 6 (15%) patients had no seizure reduction. Two of the 40 patients had hypothalamic hamartomas and were treated with unilateral mammillothalamic tract DBS; both patients had favorable results with seizure reduction of 86% and 100%. Eight of the 40 patients, from 6 different studies, had DBS electrodes placed in the anterior thalamic nucleus (ATN) bilaterally; there was seizure reduction in 6 of the 8 patients, with seizure reduction ranging from 37% to 90% [31].

Finally, regarding TMS, a review and meta-analysis of 12 studies concluded that the use of low-frequency (≤1 Hz) repetitive transcranial magnetic stimulation (TMS) for the treatment of drug-resistant epilepsy resulted in a 30% reduction in frequency of crises. Moreover, treatment of patients <21 years of age was associated with a more favorable response compared with treatment of patients older than 21 years of age. This result can be explained due to neural plasticity or decreased likelihood for entrenched and maladaptive structural changes present in adolescents. Furthermore, it is a very well-tolerated therapy, with only 17% to 23% of the participants reporting side effects, with headache being the most common (60%) [32].

DISCUSSION

Pharmacological treatment

The present systematic review aimed to present the therapeutic possibilities for the treatment of childhood epilepsy, based on an electronic search of the pertinent literature. Anti-epileptic drugs (AEDs) are the most used treatment for epilepsy. They can stop seizures from happening by changing the levels of chemicals in the brain. Around 70% of individuals with epilepsy can become seizure-free and go into long-term remission after starting the use of AEDs in monotherapy [5]. Considering seizure control and treatment retention, for individuals with partial seizures, carbamazepine, lamotrigine and levetiracetam seem to be the best treatment options whereas for individuals with generalized tonic-clonic seizures (with or without other seizure types), sodium valproate, lamotrigine and levetiracetam seem to be the best treatment options [4]. Moderate-quality evidence suggests that lamotrigine is likely to be a more effective drug than carbamazepine in terms of treatment retention (treatment failure for any reason related to treatment or due to adverse events). However, high-quality evidence provided by this review suggests that individuals are likely to achieve earlier remission and later recurrence when taking carbamazepine compared to lamotrigine.

Therefore, a choice between these two first-line treatments for individuals with new onset focal seizures must be carefully considered, taking the personal circumstances of an individual into account. On the other hand, there is evidence that carbamazepine may exacerbate some generalized seizure types so should be used with caution in individuals with this seizure type. Lamotrigine may be an effective treatment option for new onset generalized seizures, but more evidence is required to confirm this [8]. When comparing carbamazepine to topiramate, moderate-certainty evidence suggests that carbamazepine may be a more effective drug for individuals with new-onset focal seizures in terms of treatment retention (treatment failure due to lack of efficacy, or adverse events, or both occurred later with carbamazepine) and that these individuals may achieve a year of remission from seizures earlier with carbamazepine than with topiramate. At the same time, topiramate may be an effective alternative treatment option to sodium valproate for new-onset generalized seizures, but more evidence is required to confirm this [9]. When comparing carbamazepine to phenobarbital, Moderate-to low-quality evidence points to an association between treatment efficacy and seizure type in terms of seizure recurrence and seizure remission, with an advantage for

phenobarbitone for focal seizures and an advantage for carbamazepine for generalized seizures. However, as stated earlier, carbamazepine can worsen certain generalized seizure types and behavioral-related adverse events have been associated with phenobarbitone, particularly in children, thus caution and careful monitoring are required if these drugs are chosen for these specific subgroups of patients [10].

It is known that phenytoin is no longer considered to be a first line treatment in the USA and Europe due to concerns over adverse events, however, when compared to the use of phenobarbital as monotherapy in the treatment of epilepsy, Phenytoin is significantly less likely to be failed as a treatment, which may make it the preferred choice of the two drugs [5, 11]. With regard to the use of oxcarbamazepine or phenytoin as monotherapy for individuals with focal onset seizures, moderate-quality evidence suggests that oxcarbazepine may be superior to phenytoin in terms of treatment failure for any reason, seizure recurrence and seizure remission. Therefore, where first-line recommended treatments are not suitable for an individual and where an alternative treatment option is required, oxcarbazepine may be a preferable alternative treatment than phenytoin, particularly for individuals with focal onset seizures [6]. Regarding the management of acute tonic-clonic seizures, including convulsive status epilepticus in children, there is little or very little evidence regarding the use of buccal midazolam as the first-line treatment for those situations where intravenous access is not available.

Moderate to low quality shows no clear differences between intravenous lorazepam and intravenous diazepam as the first-line intravenous drug in the management of acute tonic-clonic seizures, including convulsive status epilepticus in children. There is limited and low-quality evidence regarding the intranasal use of lorazepam or midazolam as effective alternative non-intravenous routes to stop tonic-clonic seizures. This is of particular importance in countries with a high incidence of central nervous system diseases, where children often present late and in shock, making it difficult to obtain rapid intravenous access, and where intravenous cannulae and equipment are likely to be in limited supply [13]. As for the use of additional drugs to treat refractory seizures, there is little certainty about the effectiveness of clobazam. In contrast, lamotrigine and rufinamide are effective alternatives in reducing the frequency of seizures, despite that the trials reviewed were of relatively short duration. Gabapentin is also effective in reducing seizure frequency, and doses of up to 2400 mg/day are currently recommended in the British National Formulary. Despite the effectiveness of vigabatrin, its long-term use is associated with visual field constrictions which occur in a significant number of people taking vigabatrin. Given the seriousness of such visual adverse effects, the implications of long-term vigabatrin use should still be considered before commencing vigabatrin add-on therapy [15,16,17,18,19,20]. Finally, neurosteroids are compounds possessing the ability to modulate neuronal activity and affect the physiology of the central nervous system (CNS). The anticonvulsant activity is associated with the positive modulation of GABA-A receptors. As for their use as adjuvants in the treatment of intractable seizures in the pediatric population, special attention is needed, especially in the period of the last semester of gestation up to the first several years after birth [21].

Surgical treatments

Data collected from 2010 to 2015 indicates that there are three million adults and 475 children reported active epilepsy (doctor-diagnosed epilepsy under treatment, or seizures within the past twelve months), comprising 1.2% of the population. However, approximately 40% of people with epilepsy do not respond to treatment with antiepileptic drugs, which makes them potential candidates for surgical treatment. Early surgical intervention for appropriately chosen patients with drug resistant epilepsy (DRE) offers the best opportunity to avoid a lifetime of disability and premature death, despite this, surgical treatment is still underutilized [25].

The general predictors of seizure freedom include greater extent of resection, neoplastic etiology, lesional epilepsy, and complete resection of epileptiform foci, in addition to age at surgery [3, 23]. Structural MRI remains the mainstay of presurgical evaluation, while positron emission tomography (PET), ictal single photon emission computed tomography (SPECT) and functional MRI (fMRI) approaches provide additional information for localizing the epileptogenic region [25]. Potentially-curative operations can broadly be grouped into resections (in which the epileptogenic zone is removed) and disconnections (in which the epileptogenic zone is neurologically disconnected but left in place), being lesionectomy, temporal lobectomy, extratemporal cortical resection, posterior quadrantectomy and hemispherectomy some of the examples. Following this, there are also palliative operations, such as corpus callosotomy and multiple subpial transects. Lesionectomy is the most basic form of epilepsy surgery, which refers to surgical resection of the lesion causing the seizures.

A temporal lobectomy, whose most common technique is the anterior temporal lobectomy (ATL), has been the most effective technique used due to the higher likelihood of dual pathology or an epileptogenic zone that encompasses more than solely the hippocampus and amygdala [22]. The ATL standard consists of en bloc resection or resection of individual lateral and mesial temporal structures. The removal of the lateral temporal structures provides a better visualization of the mesial structures and allows the hippocampus to be removed in block [33]. Temporal lobe epilepsy (TLE) is the main indication for this procedure, in addition to being a common cause of epilepsy in children

(estimated 10–20% of all pediatric epilepsy cases). Its etiologies in children include: mesial temporal sclerosis (MTS), low-grade tumors, cortical dysplasia, vascular malformation, gliosis, heterotopia, trauma, tuberous sclerosis and neurofibromatosis. As for extratemporal cortical resection, approaches can range from lesionectomy to multilobar resection/disconnection, with extratemporal lobe epilepsy (ETLE) being the main indication for the procedure. ETLE is the most common cause of epilepsy in children, and its etiologies include: neoplasms, tuberous sclerosis, cortical dysplasia, AVMs, porencephalic cysts, gliosis, gray matter heterotopia, trauma, and perinatal insults.

Posterior quadrant (PQ) resection/disconnection is a unique combination of treating both TLE and ETLE through a multilobar procedure. The posterior quadrant consists of the parietal, posterior temporal, and occipital lobes. Finally, Hemispheric resection/disconnection involves the isolation of an entire cortical hemisphere in cases of large, multilobar, unilateral epileptogenic zones that also involve the frontal cortex (contraindicating PQ surgery). seizure freedom rates of hemispherectomy vary between 45-90% overall and 65-85% [22, 23].

With regard to new therapies, As of 2011, the use of LITT in pediatric neurosurgery has expanded dramatically, with hypothalamic hamartomas (HH) being the main indication for this type of treatment (115 out of 179 patients, 64.2%) [26, 27]. In addition to HH, other causes of childhood epilepsy that can be treated with LITT are tuberous sclerosis complex, cavernoma, among others. In both adult and pediatric neurosurgeries, the application of LITT involves stereotactic placement of a laser ablation probe, often through a bone-based anchor bolt. LITT can be effective at ablating focal epileptic lesions, leading to seizure freedom. However, in patients with MR-negative epilepsy, there are no specific lesions to target though the epileptic focus may still be quite focal [26]. For patients with drug resistant epilepsy (DRE) who are not suitable for craniotomy surgery or who have experienced failed cranial surgery, vagus nerve stimulation (VNS) is indicated as an adjunctive therapy in DRE, in both focal and generalized cases [29, 34].

Under general anesthesia, the VNS device is generally implanted on the left side, since the right vagus nerve innervates the sinoatrial node, which leads to an increased risk of cardiac complications [30]. The effectiveness depends on epilepsy type, etiology, antiepileptic drug use, severity of the epilepsy and others [34]. Still on the child population, studies point to a higher reduction of seizures in younger patients (< 12 years at implantation) than older patients (> 12 years at implantation), with the most beneficial patient group being children aged 0–6 years. The earlier the age of seizure onset, the worse the VNS response may be because of the cumulative damage of epilepsy itself. Therefore, implantation of VNS in children may be an effective means of controlling seizures at an early stage [35]. In addition to the effect on seizures, VNS also has an impact on psychiatric comorbidities in epileptic patients and improvements in alertness, attention and psychomotor activity [29, 30].

DBS is a therapeutic option consisting of electrodes that deliver electrical stimulation in order to modulate cortical excitability, thereby reducing the frequency and severity of seizures in an adjustable and reversible manner, such as responsive neurostimulation devices and temporal lobectomy. Most commonly used to treat intractable primary generalized childhood dystonia, the potential for DBS in pediatric populations offers new hope to improve a child''s quality of life [31].

Finally, transcranial magnetic stimulation (TMS) has become an important noninvasive clinical tool for neuronal perturbation. For epilepsy phenotypes that are not amenable to resective surgical treatments, low-frequency repetitive transcranial magnetic stimulation (rTMS) has emerged as a means of suppressing cortical excitability. Low-frequency rTMS therapy has been reliably demonstrated to be a safe clinical intervention. However, its efficacy in seizure attenuation remains less well established [32].

CONCLUSION

Due to the important epidemiological burden of epilepsy in the child population, the present study seeks to demonstrate what is most recent about the pharmacological and non-pharmacological management of this condition. It is known that the drug approach is currently the most used, and that in order to choose the best AEDs, one must take into account the type of crisis, time until treatment failure, time until the first seizure, among others. Finally, the results presented regarding the safety and efficacy of non-pharmacological treatment seek to encourage the increased use of surgical techniques.

DISCLOSURES

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. Ethics approval was not required for this study

Conflict of interest

The authors declare no conflicts of interest with respect to the content, authorship, and/or publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Acknowledgment

We would like to express our special thanks to Dr. Nícollas Nunes Rabelo and to Liga Acadêmica de Neurologia e Neurocirurgia (LANNA) from School of Medicine Uniatenas, Passos, Minas Gerais, Brazil, who directly or indirectly contributed for the fulfillment of this study.

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