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SYSTEMATIC REVIEW

Levetiracetam Monotherapy in Children with Epilepsy: A Systematic Review

Amerins Weijenberg[1] · Oebele F. Brouwer[1] · Petra M. C. Callenbach[1]

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Abstract

Background Levetiracetam, a second-generation anti-epileptic drug (AED) with a good efficacy and safety profile, is licensed as monotherapy for adults and children older than 16 years with focal seizures with or without secondary generalization. However, it is increasingly being used off-label in younger children.

Objectives We critically reviewed the available evidence and discuss the present status of levetiracetam monotherapy in children 0–16 years old.

Data Sources We systematically searched the literature using PubMed, Web of Science and Embase up to August 2014 for articles on levetiracetam monotherapy in children. Keywords were levetiracetam, monotherapy and child*. The titles and abstracts of 532 articles were evaluated by AW, of which 480 were excluded. The full texts of the other 52 articles were assessed for relevance.

Results We covered one review, one opinion statement and 32 studies in this review, including four randomized controlled trials, ten open-label prospective studies, eight retrospective studies, and ten case reports. The formal evidence for levetiracetam monotherapy in children is minimal: it is potentially efficacious or effective as initial monotherapy in children with benign epilepsy with centrotemporal spikes. In all of the published studies, however, efficacy and tolerability of levetiracetam seemed to be good and comparable to other AEDs.

Conclusion The data of 32 studies on levetiracetam monotherapy in children were insufficient to confirm that levetiracetam is effective as initial monotherapy for different types of seizures and/or epilepsy syndromes. There is still an urgent need for well designed trials to justify the widespread use of levetiracetam monotherapy in children of all ages.

Key Points

Efficacy and tolerability of levetiracetam monotherapy in children, even in very young children, seems to be good.

Levetiracetam monotherapy in children remains off-label because 32 studies have yielded insufficient formal evidence for its use.

1 Introduction

Levetiracetam is a second-generation anti-epileptic drug (AED) that has been on the market since 1999 in Europe as add-on therapy for adolescents from the age of 16 years with focal epilepsy.

Levetiracetam, (*S*)-α-ethyl-2-oxo-1-pyrrolidine acetamide, is the (*S*)-enantiomer of the ethyl analogue of piracetam and shares its chemical structure with numerous nootropic drugs [1, 2]. The mechanism of action differs structurally and functionally from other currently available AEDs as it binds to the synaptic vesicle protein 2A (SV2A). The presence of SV2A in the presynaptic terminals suggests that its anti-epileptic function might be based

✉ Petra M. C. Callenbach
p.m.c.tijink@umcg.nl

[1] Department of Neurology, University Medical Centre Groningen, University of Groningen, AB 51, P.O. Box 30 001, 9700 RB Groningen, The Netherlands

on it affecting presynaptic events that regulate synaptic vesicle release [3]. Although its precise mechanism of action is not known, Nowack et al. [4] suggested that levetiracetam might modulate SV2 protein interactions. As a consequence, normal levels of SV2 and synaptotagmin (a SV2-binding protein) at the synapse are maintained, which may reduce seizures. It also plays a role in Ca^{2+} homeostasis by inhibiting ryanodine and IP3 receptor-dependent Ca^{2+} release from endoplasmic reticulum and by inhibiting Ca^{2+} entry through blocking of the L-type Ca^{2+} channels in hippocampal neurons [5].

Levetiracetam is almost completely absorbed after oral administration and its bioavailability is close to 100 %; it is unaffected by food [6]. Peak plasma concentrations occur in 1 h and steady state concentrations are achieved in 2 days if levetiracetam is taken twice daily. Pharmacokinetics is linear, dose proportional and time independent [6]. The distribution is close to the volume of intracellular and extracellular water and levetiracetam remains almost unattached to proteins [7]. Levetiracetam is minimally metabolized and, after 24 h, 27 % is excreted as inactive metabolites [8]. The metabolism of levetiracetam does not involve the hepatic cytochrome P450 (CYP) system, nor does it inhibit or induce hepatic enzymes [6]. The major elimination route for levetiracetam is renal; 66 % as an unchanged drug [9]. Dose adjustments are only recommended in patients with moderate to severe renal impairment or severe hepatic impairment with concomitant renal insufficiency. The body clearance of levetiracetam in children is 30–40 % higher compared with adults and it is therefore recommended that children have a daily maintenance dose on a weight normalized level (20–60 mg/kg/day) divided over two doses; this is equivalent to 130–140 % of the usual daily adult maintenance dosage (1000–3000 mg/day) [10]. Levetiracetam has no clinically meaningful drug–drug interactions with other AEDs, or non-AEDs such as oral contraceptives, warfarin and digoxin. Thus, because of its unique chemical structure, specific mode of action and pharmacokinetic profile, levetiracetam has become one of the most widely used second-generation AEDs for both adults and children.

Levetiracetam was licensed as add-on therapy in children in 2005. Nowadays, levetiracetam is registered in Europe and the US as add-on therapy for focal onset seizures with or without secondary generalization in patients from 1 month of age, as add-on therapy for myoclonic seizures in patients from 12 years of age with juvenile myoclonic epilepsy, and as add-on therapy for primary generalized tonic-clonic seizures in patients with idiopathic generalized epilepsy (in Europe from 12 years of age; in the US from 6 years of age).

It was not until 2006 that it was licensed as monotherapy, but only in Europe, for adults and children from 16 years of age with focal onset seizures with or without secondary generalization. Off-label use of levetiracetam as monotherapy in younger children has increased considerably over the last decade due to its efficacy in both focal and generalized seizures, its good safety profile, favourable pharmacokinetic properties and its availability in an intravenous form for the acute setting [11–18].

Here, we review the available evidence for the use of levetiracetam monotherapy in children in the literature, including data from randomized controlled trials. We also discuss the present status of levetiracetam and make some recommendations for future research.

2 Methods

For this review, a literature search was performed by AW using PubMed (Medline), Web of Science and Embase (until August 2014) for papers on levetiracetam monotherapy in children (<18 years of age). There are no Cochrane Reviews on levetiracetam monotherapy. The following search terms were used: levetiracetam AND monotherapy AND child*. Only papers written in English, Dutch, French, or German were included. Articles were screened by AW and, in case of any dispute, discussed with PMCC. If a study included both children and adults, it was reviewed only if the results of efficacy were reported separately for children. We also searched the reference lists of these publications for more articles relevant to the topic. Abstracts of congress proceedings were not included. Data extraction from the articles was done independently by AW in Word and monitored by PMCC. We critically evaluated the study designs and whether there was any risk of bias in the individual studies.

3 Overview of Published Articles

The systematic literature search yielded 690 articles. After removing duplicates, the titles and abstracts of 532 articles were evaluated by AW; 480 were excluded (Fig. 1). The full texts of the other 52 articles were assessed for relevance and 34 articles were included in this systematic review: four randomized controlled trials (RCTs), ten open-label prospective studies, eight retrospective studies, ten case reports, a review, and an opinion statement [12, 19–51].

3.1 Review, Opinion Statement and Case Reports

One review and one opinion statement argued that levetiracetam monotherapy should be the drug of choice in patients with juvenile myoclonic epilepsy, based on evidence from trials, especially if valproic acid is contra-

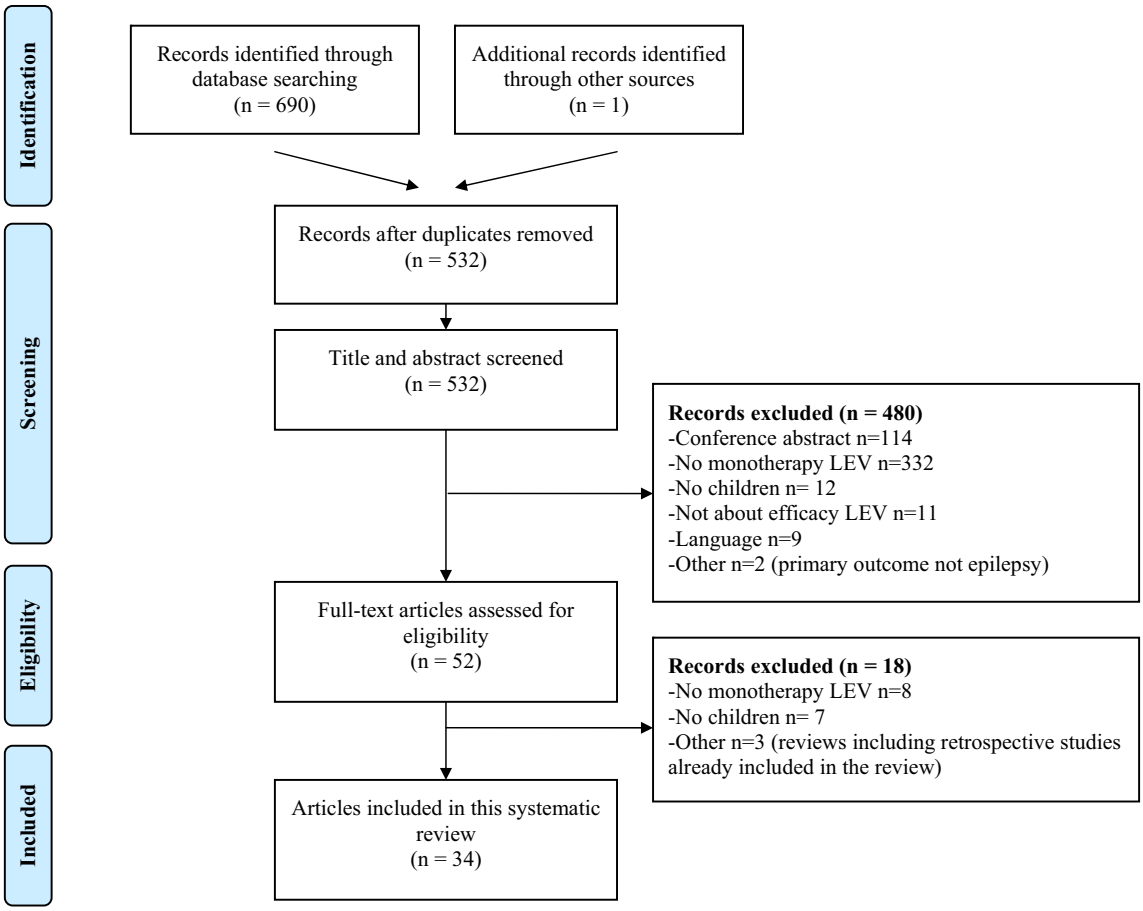

Fig. 1 PRISMA flow diagram. *LEV* levetiracetam

indicated; for example, in women of child-bearing age [50, 51].

Ten case reports have been published on the use of levetiracetam monotherapy in children, including neonates, with a wide variety of seizure types, epilepsy syndromes, dosages and ages (Table 1) [40–49]. Dosages of levetiracetam were given in mg/kg/day or mg/day or not documented. All children became seizure-free, but the duration of follow-up was not given in three case reports (Table 1). The case reports suggested a high efficacy of treatment with levetiracetam monotherapy, and adverse events were infrequent or they were not reported.

3.2 Retrospective Studies

Eight retrospective studies on levetiracetam monotherapy in children have been published, the first in 2004 (Table 2) [32–39]. Most of them included patients with focal and/or generalized epilepsy. Levetiracetam dosage in these studies ranged from 10 to 108 mg/kg/day, but was mostly in the 20–40 mg/kg/day range. The mean duration of follow-up ranged from 3 to 27 months; four studies had a follow-up of more than 1 year [34, 35, 37, 38]. Three studies compared efficacy and tolerability of levetiracetam with carbamazepine [35], with oxcarbazepine or valproic acid [36], and with valproic acid [38].

In all but one of the eight studies, levetiracetam efficacy was considered to be good, and seizure freedom was achieved in more than 60 % of patients in most studies, including those on children who had been using another AED prior to levetiracetam monotherapy (Table 2). Tolerability was good in all studies, with behavioural and cognitive changes being the most common adverse events; the discontinuation rate due to adverse events was low (0–12 %). In one study, the retention rate was not significantly different between the two groups (levetiracetam vs oxcarbazepine and levetiracetam vs valproic acid), although levetiracetam monotherapy failed more often due to lack of efficacy in both groups [36].

3.3 Prospective Open-Label Studies

Lagae et al. [12] were the first to report a prospective trial on levetiracetam monotherapy in children. Since then, nine more open-label prospective studies have been published that included children, and sometimes even neonates, with

Table 1 Case reports on levetiracetam monotherapy in children (10 studies)

References	Diagnosis	Number of children	Age (years)[a]	Maximum dosage	Follow-up of monotherapy (months)	Efficacy	AEDs prescribed before levetiracetam
Bello-Espinosa and Roberts [40]	BECTS	3	4	250 mg/day	ND	SF	None
			6	1000 mg/day		SF	
			10	500–1000 mg/day		SF	
Kossoff et al. [41]	Landau–Kleffner syndrome	1	5	500–750 mg/day (60 mg/kg)	9	SF	CBZ, VPA
Shoemaker and Rotenberg [42]	Neonatal seizures	3	0	30 mg/kg/day	ND	SF	PHB, MDZ, fos-PHT
			0	30 mg/kg/day		SF	PHB, MDZ, fos-PHT
			0	30 mg/kg/day		SF	fos-PHT, OXC
Papacostas et al. [43]	Tuberous sclerosis	1	7	1000 mg/day	18	SF	VPA, OXC, CBZ, TPM
Alehan et al. [44]	PRES → non-convulsive status epilepticus	1	10	20 mg/kg/day	9	SF	PHT
García and Rubio [45]	Panayiotopoulos syndrome	2	8	2000 mg/day	36	SF	VPA
			12	1000 mg/day	36	SF	VPA
Ledet et al. [46]	Neonatal seizures	1	0	40 mg/kg/day	8	SF	PHB
Harbord [47]	Hemiplegic cerebral palsy and epilepsy	3	8	ND	24	SF	LTG, TPM, VPA
			14	ND	36	SF	CBZ, LTG, VPA
			17	ND	36	SF	CBZ, LTG, PHB, VPA
Arslan et al. [48]	Acquired epileptiform opercular syndrome	1	5	50 mg/kg/day	ND	SF	None
Verrotti et al. [49]	Epilepsy in patient with Cornelia de Lange syndrome	1	ND	ND	60	SF	None

AEDs anti-epileptic drugs, *BECTS* benign epilepsy with centrotemporal spikes, *CBZ* carbamazepine, *fos-PHT* fosphenytoin, *LTG* lamotrigine, *MDZ* midazolam, *ND* no data, *OXC* oxcarbazepine, *PHB* phenobarbital, *PHT* phenytoin, *PRES* posterior reversible encephalopathy syndrome, *SF* seizure free, *TPM* topiramate, *VPA* valproic acid

[a] Age at start treatment

Table 2 Retrospective studies on levetiracetam monotherapy in children (8 studies)

References	Diagnosis	Number of children	Age (years)[a]	Dosage (mg/kg/day)	Follow-up of monotherapy (months)	Efficacy (%)	% AE (% stopped due to AE)	% patients with AEDs before LEV
Koukkari and Guarino [32]	Focal or generalized epilepsy	19	0.8–16	20–79	ND	SF or >50 % SR 58	33 (10)	0
Khurana et al. [33]	Focal or generalized epilepsy	18	2.5–18	14–60	Mean 10.4	SF 61, >50 % SR 67	22 (11)	89
Sharpe et al. [34]	JME	30	8–23	10–59	Mean 27	SF 80	7 (3)	60
Perry et al. [35]	Focal epilepsy	LEV 66	2.8–7.8[b]	ND	Mean 17.1	SF 73 (at 6 months)	45 (12)	19.7
		CBZ 20	3.4–9.3[b]	ND	Mean 18.5	SF 65 (at 6 months)	70 (5)	5
Bertsche et al. [36]	Focal epilepsy	LEV 42	0.5–16.7	27–108	12	Ret. LEV 50	LEV 10 (10)	0
		OXC 34	1.9–16.9	11–71		Ret. OXC 71[d]	OXC 12 (12)	
	Focal or generalized epilepsy[c]	LEV 61	0.5–16.7	27–108	12	Ret. LEV 52	LEV 7 (7)	0
		VPA 49	0.5–16.3	5–47		Ret. VPA 63[d]	VPA 14 (14)	
Chen et al. [37]	ESES	21	1.1–11.7[e]	30–60[e]	19[e]	Reduction of SWI >50 % 29	ND (0)[e]	ND
						Reduction of SWI <50 % 33		
Xiao et al. [38]	BECTS	LEV 33	4–11.3	15–38	18	SF 6 months 58	27 (0)	0
						SF 18 months 100		
		VPA 23	4–13.5	9–31	18	SF 6 months 61[d]	22 (0)[d]	
						SF 18 months 100[d]		
Bayram et al. [39]	Focal or generalized epilepsy	9	10–16	20–50	Mean 7	SF 100	0 (0)	100

AE adverse events, *AEDs* anti-epileptic drugs, *BECTS* benign epilepsy with centrotemporal spikes, *CBZ* carbamazepine, *ESES* electrical status epilepticus during sleep, *JME* juvenile myoclonic epilepsy, *LEV* levetiracetam, *ND* no data, *OXC* oxcarbazepine, *Ret.* retention rate, *SF* seizure free, *SR* seizure reduction, *SWI* spike-wave index on the electroencephalogram, *VPA* valproic acid

[a] Age at start treatment

[b] Interquartile range

[c] Absences were not included

[d] Not significantly different compared with LEV

[e] Total population, including both add-on and monotherapy

different but overall relatively benign seizure types and/or epilepsy syndromes (Table 3) [23–31]. In three studies, levetiracetam was given in mg/day, without considering body weight, with dosages ranging from 1000 to 3000 mg/day [23, 24, 27]. In seven studies, dosages were based on bodyweight, starting with 10 mg/kg/day, with increasing dosage until seizure freedom was reached, with a maximum of 70 mg/kg/day (Table 3) [12, 25, 26, 28–31]. In a pilot study by Kossoff et al. [26], children were switched from carbamazepine or oxcarbazepine monotherapy to levetiracetam monotherapy. The baseline AED was tapered off over 2 weeks. Verrotti et al. [24] reported on 21 children who received levetiracetam monotherapy: 12 of them were converted from monotherapy with valproic acid, carbamazepine, oxcarbazepine, or lamotrigine to levetiracetam monotherapy. However, follow-up was more than 1 year in only half of these trials; this is regarded as the minimum duration to draw any conclusions about long-term efficacy, adverse events and tolerability of AED treatment [52, 53].

In most studies, efficacy of levetiracetam monotherapy was reported to be good, with a high percentage of children becoming seizure free (20–100 %) or having more than 50 % seizure reduction (62–100 %). In one study, the response was significantly better in the children who were AED-naive before initiating treatment with levetiracetam [24]. Some studies used extra outcome parameters other than efficacy, such as quality of life [12], electroencephalography (EEG) findings and language function [26]. Lagae et al. [12] studied ten children and observed increased alertness in three and a positive effect on behaviour in one. Furthermore, median overall quality of life was higher in children on levetiracetam monotherapy than in children with add-on levetiracetam [12]. Kossoff et al. [26] evaluated EEG findings and language function in six children with benign epilepsy with centrotemporal spikes (BECTS), and they also looked for additional evidence of impaired auditory comprehension and verbal memory. After 6 months of treatment, the parents of all children reported subjective improvements, which were confirmed in most children by objective testing. The EEG had normalized in only three children.

Six trials reported the occurrence of adverse events, most commonly irritability and somnolence [12, 24, 26, 28, 29, 31]. In three, all adverse events were transient [24, 28, 29] and in two, none of the children discontinued levetiracetam because of adverse events [12, 26]. In a large study of 37 children on levetiracetam monotherapy and 83 children on levetiracetam add-on treatment, a relatively high percentage reported adverse events (47.5 %) and four of them even had to discontinue levetiracetam [31]. Results for the group treated with monotherapy were, however, not given separately.

3.4 Randomized Controlled Trials

Four RCTs have been published: two open-label parallel group trials and two double-blind trials (Table 4) [19–22]. Most trials only included children with a well described epilepsy syndrome such as BECTS [19, 22] or absence epilepsy (childhood absence epilepsy [CAE], juvenile absence epilepsy [JAE]) [20]. The age at enrolment varied between 3 and 17 years. The maximum dosage of levetiracetam was 2000 mg/day in 12- to 17-year-old children [21] or 30 mg/kg/day [19, 20, 22]. One trial was placebo-controlled [20] and, for obvious ethical reasons [54], the duration of the double-blind period was only 2 weeks, which is much shorter than the duration of the other trials (24–78 weeks).

The equivalence open-label trial of Coppola et al. [19] compared levetiracetam with oxcarbazepine in children with BECTS and they observed no significant difference in the percentage being seizure free at 18 months (Table 4). In another trial, in children with absence epilepsy, Fattore et al. [20] showed no significant difference in seizure freedom between levetiracetam and placebo. After the 2-week double-blind period, the trial continued as an open-label trial and almost all children receiving the placebo were switched to levetiracetam. During long-term follow-up, 32 % (12/38) of the children initially on levetiracetam continued with levetiracetam and were seizure-free for at least 267 days; 63 % (24/38) discontinued levetiracetam because of inefficacy at a later stage. After 1 year, 17 children (29 %) were still seizure-free on levetiracetam (initially on levetiracetam or placebo therapy). Rosenow et al. [21] included patients aged ≥12 years with newly diagnosed focal or generalized epilepsy. If patients were already using an AED, this was tapered off during the first 3 weeks of the study period. A post-hoc subgroup analysis was performed for 33 patients aged 12–17 years. Seizure freedom after 6 weeks of treatment was compared between levetiracetam and lamotrigine, although patients on lamotrigine were still in their titration period and the dosage of lamotrigine also increased after this time-point. Efficacy and tolerability of levetiracetam and lamotrigine did not differ significantly for the group aged 12–17 years. Quality-of-life scores (QOLIE-10) at the beginning and end of treatment (26 weeks) were similar in both treatment groups; a subgroup analysis for children aged 12–17 was not presented. In the non-inferiority trial of Borggraefe et al. [22], levetiracetam was compared with sulthiame in children with BECTS. Their primary endpoint was treatment failure, defined by seizure recurrence during the observation period. This was not significantly different between treatments (Table 4). However, the retention rate was significantly higher in the sulthiame group than in the levetiracetam group ($p = 0.03$).

Table 3 Prospective open-label studies on levetiracetam monotherapy (10 studies)

References	Trial design	Diagnosis	Number of children	Age (years)[a]	Dosage[b]	Follow-up	Efficacy (%)	% AE (% stopped due to AE)	Retention rate (%)
Lagae et al. [12]	OL	All seizure types	10	4–14	17–47	20 weeks	SF 20, >50 % SR 90	10 (0)	90
Di Bonaventura et al. [23]	OL	Idiopathic generalized epilepsy	4	8–16	2000–3000 (mg/day)	6–10 months	SF 100	0 (0)	ND
Verrotti et al. [24]	OL, MC	BECTS	21	5–12	1000–2500 (mg/day)	12 months	SF or >50 % SR 100	9.5 Transient (0)	100
Gümüş et al. [25]	OL	West syndrome	5	0	30–60	4 weeks	SF 40, >50 % SR 80	ND	100
Kossoff et al. [26]	OL	BECTS + language problems	6	6–12	40	6 months	SF 67, improvement in language function	17 (0)	100
Verrotti et al. [27]	OL, MC	JME	32	7–16	1000–2500 (mg/day)	12 months	SF 91, >50 % SR 100	0 (0)	100
Verrotti et al. [28]	OL, MC	CAE, JAE	21	5–13	31–70	6 months	SF 52	10 Transient (0)	ND
			12			12 months	SF 100		
Verrotti et al. [29]	OL, MC	COE-G	12	6–16	20–45	18 months	SF 100	17 Transient (0)	100
Fürwentsches et al. [30]	OL	Neonatal seizures	6	0	10–50	3 months	SF 100 after 6 days, SF 50 after 3 months	0 (0)	ND
Li et al. [31]	OL	All seizure types	37	0–16[c]	10–60	12 months	SF 46, >75 % SR 62	47.5 (3.3)[c]	73.3[c]

AE adverse events, *BECTS* benign epilepsy with centrotemporal spikes, *CAE* childhood absence epilepsy, *COE-G* childhood occipital epilepsy–Gastaut type, *JAE* juvenile absence epilepsy, *JME* juvenile myoclonic epilepsy, *MC* multicentre, *ND* no data, *OL* open label, *SF* seizure free, *SR* seizure reduction

[a] Age at start treatment

[b] Dosage in mg/kg/day unless stated otherwise

[c] Total population, including both add-on and monotherapy

Table 4 Randomized controlled trials on levetiracetam monotherapy (4 studies)

References	Trial design	Diagnosis	Number of children	Age (years)[a]	Dosage[b]	Follow-up	Efficacy (%)	% AE (% stopped due to AE)	Retention rate (%)
Coppola et al. [19]	RCT, OL, PG	BECTS	LEV 21	3–14	LEV 20–30	18 months	LEV SF 90[c]	LEV 14 (5)	LEV 85.7
			OXC 18		OXC 20–35		OXC SF 72	OXC 11 (5.5)	OXC 66.7
Fattore et al. [20]	RCT, DB, PC, MC	CAE, JAE	LEV 38	4–15	LEV 30	2 weeks	LEV SF 24[c] (18 % also on EEG)	LEV 18	LEV 97.4
			Placebo 21				Placebo SF 5 (0 % on EEG)	Placebo 14	Placebo 100
Rosenow et al. [21]	RCT, OL, PG, MC	Focal and generalized epilepsy	LEV 17	12–17	LEV 1500–2000 (mg/day)	6 weeks	No difference	No differences	ND
			LTG 16		LTG 150–200 (mg/day)	26 weeks	LEV vs LTG	LEV vs LTG	
Borggraefe et al. [22]	RCT, DB, PG, MC	BECTS	LEV 21	6–12	LEV 20–30	24 weeks	LEV TF 19[c]	LEV (23.8) vs STM[c] (4.5[c])	LEV 57.1
			STM 22		STM 4–6		STM TF 9.1	Except for airways: LEV 23.8	STM 86.4 ($p = 0.03$)
								STM 63.6 ($p = 0.014$)	

AE adverse event, *BECTS* benign epilepsy with centrotemporal spikes, *CAE* childhood absence epilepsy, *DB* double blind, *EEG* electro-encephalography, *JAE* juvenile absence epilepsy, *LEV* levetiracetam, *LTG* lamotrigine, *MC* multi centre, *ND* no data, *OL* open label, *OXC* oxcarbazepine, *PC* placebo controlled, *PG* parallel group, *RCT* randomized controlled trial, *SF* seizure freedom, *STM* sulthiame, *TF* treatment failure

[a] Age at start treatment

[b] Dosage in mg/kg/day unless stated otherwise

[c] Not significantly different

The most commonly reported adverse events were somnolence and irritability or behavioural problems. Significant differences with respect to adverse events were not observed between the treatments reported. However, none of the trials used a standardized questionnaire to investigate the occurrence of adverse events.

4 Discussion

In this review, 32 studies on levetiracetam monotherapy in children are described. In all of them, efficacy and tolerability of levetiracetam monotherapy seems to be good and comparable or even favourable to other AEDs. Nonetheless, we must recognize that it has only been licensed for monotherapy in children older than 16 years in Europe.

4.1 Current Evidence for Efficacy

The most commonly used primary endpoint for efficacy was seizure freedom and/or percentage of seizure reduction (30 of 32 studies). The case reports suggested a very high efficacy of treatment with levetiracetam monotherapy. Publication bias may, however, have led to an unrealistic positive view of its efficacy. The percentage of children becoming seizure-free in both retrospective and prospective studies was 61–100 %. Only 20–46 % of cases became seizure-free in three prospective open-label studies that included children with all seizure types or even West syndrome [12, 25, 31]. Efficacy of levetiracetam does not seem to be related to age at enrolment, dosage or seizure type and/or epilepsy syndrome (Tables 1, 2, 3, 4). Since most studies included children with overall relatively benign seizure types and/or syndromes, its efficacy might be overestimated. In summary, the efficacy of levetiracetam monotherapy in children seems good and comparable to other AEDs, but the level of evidence is limited and not available for all seizure types and/or epilepsy syndromes.

4.2 Current Knowledge on Tolerability

The range of children with reported adverse events varied between 0 and 47.5 %. The percentage of children who had to stop levetiracetam treatment due to adverse events was 0–12 % in most studies, although in the trial of Borggraefe et al. [22], 23.8 % of the children discontinued levetiracetam because of adverse events. The most frequently reported adverse events were behavioural and/or cognitive changes (i.e. irritability, mood disturbances or somnolence), but these complaints were mostly transient. This is in line with the most commonly reported adverse events for levetiracetam [55]. In children with pre-existing behavioural problems, the problems could be exacerbated during levetiracetam therapy [56]. In some, but not all, of the prospective studies, pre-existing behavioural and/or cognitive problems were exclusion criteria [24, 26–29]. In two RCTs, children with a mental deficit or intellectual disability were excluded [19, 20]. The other two RCTs did not mention any exclusion criteria for behavioural and/or cognitive problems [21, 22]. Because children with epilepsy may develop cognitive and/or behavioural problems due to both the epilepsy itself and the treatment with AEDs, it is very important to evaluate the exact role of treatment on these problems as well [54, 57]. According to Cross et al. [58], effective management requires treatment within the context of the overall health status and quality of life of the treated child. Two trials investigated quality of life, and this was unchanged or positively influenced by the use of levetiracetam monotherapy [12, 21].

In summary, the tolerability of levetiracetam seems to be good, with only a few adverse events that are mostly transient, even in very young children and in dosages up to 70 mg/kg/day.

4.3 Evaluation of Study Design and Methodology

According to the International League Against Epilepsy (ILAE), the best evidence for the use of levetiracetam monotherapy in children up to March 31, 2012 reached level D for children with BECTS, based on the study by Coppola et al. [19, 53]. Level D means there is one class III double-blind or open-label study, or one or more class IV clinical studies or data from expert committee reports or opinions from experienced clinicians [53]. Since 2012, two more RCTs on levetiracetam monotherapy have been published, both with a class III rating [21, 22]. Because of the inconclusive trial results of Borggraefe et al. [22], the level of evidence for levetiracetam monotherapy in BECTS did not reach level C, while the trial results of Rosenow et al. [21] could not contribute to the level of evidence for levetiracetam monotherapy in focal and generalized epilepsy because of their study design.

Prospective studies may also contribute to the level of evidence. However, eight of the ten prospective studies did not perform a formal statistical evaluation, and only one of the other two studies found a significant decrease in seizure frequency in a subgroup analysis [12, 23–31]. Although these ten studies did not contribute to the level of evidence for levetiracetam monotherapy in children, the percentage of children becoming seizure-free after the start of levetiracetam is promising, although there may well be some publication bias.

The reasons for the small number of prospective trials performed in children are pharmaceutical companies' lack of interest in such a small market when the patent has expired, and the difficulties in recruiting patients, partially

due to ethical and legal aspects [59]. Moreover, in the past, separate drug trials in children were not required. As a consequence, levetiracetam is often prescribed off-label for children based on the results of trials in adults. Children, however, have a different developmental physiology, disease pathophysiology, pharmacokinetics and/or pharmacodynamics, resulting in treatment responses that are unpredictably different from those in adults [60, 61]. There is therefore an urgent need for clinical trials in children, because <50 % of medicines used in children have been properly studied in this age group [62]. For example, antiepileptic drugs that have been registered as add-on therapy in children and/or as monotherapy in adults should also be studied as monotherapy in children; this is already obligatory for drugs now being developed.

The ILAE has described an ideal design for clinical trials in children [53]. This includes a randomized double-blind design, with adequate sample size calculations leading to a large enough study population to show non-inferiority with a ≤20 % relative difference between treatment arms, based on 80 % power in a non-inferiority analysis versus an acceptable comparator; with retention rate or seizure freedom as the primary endpoint after a minimum of 48 weeks of treatment, and an appropriate statistical analysis. Of the four RCTs on levetiracetam in children, only two were double-blind studies [19, 22]. Remarkably, these two studies compared levetiracetam with oxcarbazepine or sulthiame in children with BECTS, whereas the level of evidence for the efficacy of both oxcarbazepine and sulthiame is low [19, 22, 53]. Carbamazepine and valproic acid would have been a more obvious choice for comparison of efficacy [53]. Furthermore, the follow-up duration in the Borggraefe et al. [22] study was only 24 weeks.

In our opinion, one of the best ways to measure efficacy, side effects and tolerability is by using retention rate, because this endpoint combines all these parameters [52]. Retention rates in the prospective open-label studies and RCTs ranged from 57.1 to 100 % (Tables 3, 4).

One limitation of our review is that we did not include conference papers and that the literature search and screening of articles was done by only one person. Another is that we did not perform a meta-analysis. This was not possible due to the heterogeneity of the population with varying epilepsy syndromes and seizure types, the variation in study designs and the different AEDs used for comparison.

5 Conclusion and Recommendations

The formal evidence for the use of levetiracetam monotherapy in children remains quite scarce: it is potentially efficacious or effective as initial monotherapy in children with BECTS. Because of the study designs and the limited number of trials, there is insufficient data available to confirm that levetiracetam is effective as initial monotherapy in children for different types of seizures and/or epilepsy syndromes, other than BECTS.

More importantly, however, in the studies we evaluated, the efficacy of levetiracetam monotherapy in children seems at least equally comparable to other AEDs. The spectrum of reported adverse events is favourable, and levetiracetam does not have a negative impact on cognition [63]. Together with its availability in an intravenous form, unique chemical structure, novel mode of action and pharmacokinetic profile, levetiracetam may become one of the most important AEDs in treating children with epilepsy.

To formally justify the widespread use of levetiracetam monotherapy in children of all ages, we need more well conducted, double-blind RCTs to evaluate the efficacy, side effects and tolerability of levetiracetam monotherapy in children.

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We confirm that this article does not contain any studies with human participants performed by any of the authors.

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