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Review

Behavioral side-effects of levetiracetam in children with epilepsy: A systematic review



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ABSTRACT

Purpose: Children with epilepsy are more likely to have behavioral problems compared to children without epilepsy. Literature suggests that levetiracetam leads to behavioral side-effects in children with epilepsy. The objective of this study is to provide a better overview of the frequency and variety of behavioral side-effects, which can be initiated by levetiracetam therapy in children with epilepsy.

Method: Electronic databases used in the search were PubMed, Medline, Cochrane and Embase. Studies were eligible for inclusion when they included children from one month to 18 years of age with a diagnosis of epilepsy, used levetiracetam, had other AEDs on a stable regimen for at least two months, reported about behavioral side-effects and had a follow-up of at least two weeks. Quality assessments and data collection were carried out for all eligible studies.

Results: Thirteen studies, including 727 patients using levetiracetam, were included in this systematic review. Three randomized controlled trials showed a total of 62 behavioral side-effects in 203 patients, effects which led to discontinuation of levetiracetam in only two of 102 patients (2.0%). Hostility, nervousness and aggression were reported mostly. Meta-analysis showed a statistically significant relative risk of 2.18 for the total number of behavioral side-effects for levetiracetam versus placebo. Observational studies showed mixed results with both behavioral deteriorations and improvements following levetiracetam.

Conclusion: Based on the findings in this systematic review, children using levetiracetam have a risk of developing several behavioral side-effects such as aggression, hostility and nervousness compared to children who do not use levetiracetam.

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1. Introduction

Epilepsy is a common neurological disorder with a peak incidence in childhood affecting four to ten children per 1000.^{1,2} Childhood-onset epilepsy is associated with mental retardation, developmental disabilities, behavioral problems and psychosocial problems in the long term.^{1,3} Psychiatric comorbidity such as autism, attention-deficit hyperactivity disorder, conduct problems,

depression and anxiety are eight to 23 percent more likely to occur in children with epilepsy compared to children without epilepsy.² Despite the fact that various antiepileptic drugs are known to initiate or worsen already existing behavioral problems, they are still the mainstay of treatment in children with epilepsy.³ Behavioral problems, ranging from mild to severe, may be exerted by any anti-epileptic drug (AED). Other factors, such as patients' characteristics and poly- or monotherapy with AEDs, also have an influence on the expression and severity of these behavioral problems.^{3,4} Polytherapy with AEDs may lead to a higher risk of developing side-effects, including behavioral side-effects, compared to monotherapy.³

Levetiracetam is a second-generation antiepileptic drug that has been approved for the treatment of epilepsy in both children and adults. This anticonvulsant drug has a unique mechanism

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which involves binding to the synaptic vesicle protein 2A resulting in a possible effect on neurotransmitter release from these presynaptic vesicles, although the exact mechanism of action is still unknown.^{5,6} In children, the recommended dose for levetiracetam is 10–60 mg/kg/day compared to 1000–3000 mg/day in adults. The pharmacokinetics in children differs only slightly from in adults, characterized by a faster elimination rate.^{7,8} The daily maintenance dose of levetiracetam children should be 130–140% of the daily dose used in adults due to the 30–40% higher plasma clearance. But this dose should be corrected for body weight and given in divided doses in children.⁷

Levetiracetam treatment in adults has a proven efficacy in both localization-related and generalized epilepsies.^{9–19} This is also proven in children with localization-related and generalized epilepsies.^{20–29} Behavioral side-effects of levetiracetam have been frequently reported and consist of a variety of behavioral problems, including aggression as well as changed mood states such as depression, agitation, hostility, irritability and hyperexcitability.³⁰ Commonly the reported behavioral side-effects are of an activating-type; ‘uppers’ as described by Ketter et al. and Roberts et al.^{31,32} Such effects may lead to early discontinuation of levetiracetam resulting in an inadequate seizure control.³³ However, only a few studies systematically report the behavioral side-effects of levetiracetam in children.

The objective of this study is to provide a better overview of the frequency and variety of behavioral side-effects of levetiracetam therapy in children with epilepsy. We will, therefore, review the existing literature systematically.

2. Methods

2.1. Search strategy

In October 2013 and March 2014 a search was conducted in PubMed, Medline, Cochrane and Embase. Subsequently the reference lists of relevant articles were reviewed to search for additional relevant studies. The major search terms included children, epilepsy, levetiracetam and behavior. A complete overview of the search

strategy in PubMed is provided in the [Appendix A](#). When possible a couple of limits were used concerning language (English, Dutch or German), age (one month–18 years), journal articles and original trials.

2.2. Selection criteria

Studies were eligible for inclusion when they met the following criteria: children from one month to 18 years of age, diagnosis of epilepsy, using levetiracetam mono- or add-on therapy, follow-up of at least two weeks and reporting about behavioral side-effects. Exclusion criteria were: studies concerning children and adults without subgroup analyses for children, case reports (<10 patients), studies written in a language other than English, Dutch or German, studies reporting neonatal convulsions or intravenous therapy with levetiracetam. The search and selection of eligible studies were carried out by three authors (EH, AL, MM).

2.3. Review methods

Quality assessments and data collection were performed for all eligible studies using a standardized form taking the risk of bias into account. Data collection included study design, demographic information on patients including type of epilepsy, blinding, randomization, dose of levetiracetam, duration of treatment and follow-up and number of reported behavioral side-effects. When behavioral side-effects were reported we analyzed behavioral problems in general including aggression and changed mood states such as hostility, agitation, irritability, hyperactivity, nervousness, restlessness, emotional lability, impulsiveness as well as psychiatric effects such as anxiety states, depression, dysphoria or psychosis.

2.4. Data analysis

The numbers of behavioral side-effects reported in patients from the included studies were counted. Subsequently we defined subgroups to look at the number of behavioral side-effects in

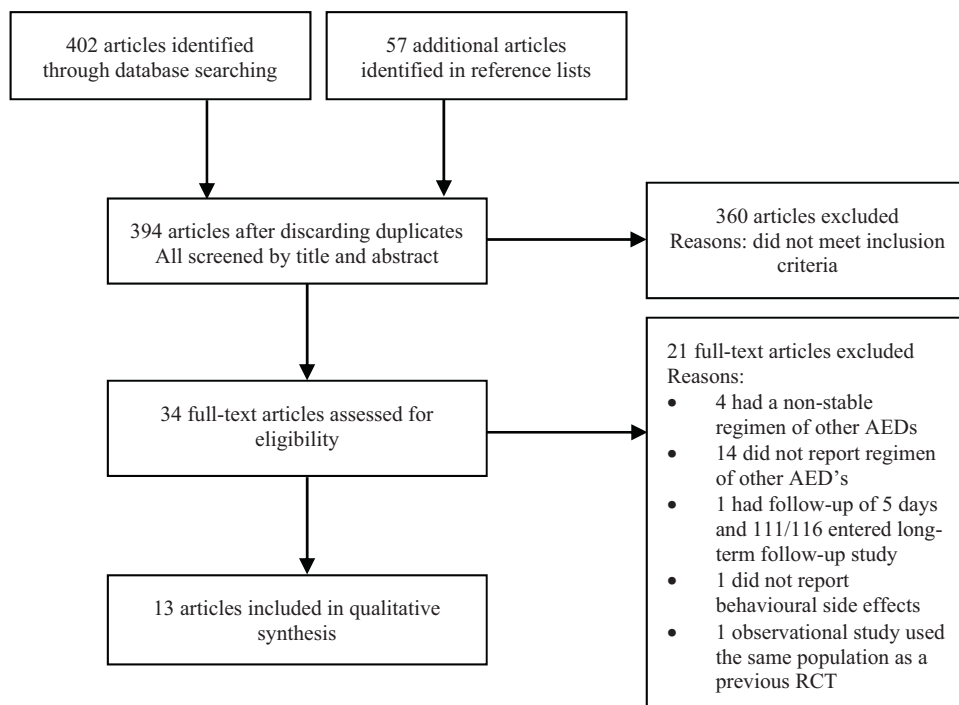


Fig. 1. Flow-diagram of study identification and selection.

patients receiving levetiracetam add-on or monotherapy. SPSS was used to perform a Chi-square or Fisher's exact test to compare the number of (specific) behavioral side-effects between patients using levetiracetam and patients using placebo, $p < 0.05$ indicating statistical significance. A meta-analysis for total number of behavioral side-effects was performed using Review Manager 5 software. Statistical heterogeneity was assessed by describing I^2 . Values of 25% were considered as low heterogeneity, 50% as moderate heterogeneity and 75% as high heterogeneity.³⁴

3. Results

3.1. Study selection

The flow diagram in Fig. 1 describes the process of study selection. Database searching and reviewing the reference lists identified 394 articles after duplicates were removed. Of these 360

did not meet inclusion criteria leaving 34 articles to be fully assessed by using the entire text. Studies were excluded when it was not clear if the other AEDs were on a stable regimen during the study period with levetiracetam. Schiemann-Delgado et al.³⁵ performed a long-term open-label extension study which includes a large part (80/98) of the study population used by Levisohn et al.²⁶ We, therefore, decided to exclude this study and not to use the reported side-effects.³⁵ Eventually a total of thirteen articles met the eligibility criteria and were included in the review. The study characteristics are shown in Table 1.

3.2. Risk of bias in included studies

Only three studies were randomized, placebo-controlled and double-blind leading to a low risk of selection and information bias.^{26–28} However, two out of three did not describe who were blinded to the intervention.^{26,28} In nine studies all participants

Table 1
Study characteristics of included studies.

Study	Study design	LEV therapy	Diagnosis ^a	Ages	Dosage (mg/kg/d) (mean)	Follow-up (mean)	Behavioral side-effect
Lagae (2003) ³⁶ (n = 21)	Prospective, open-label	Add-on	Localization-related epilepsies and generalized epilepsies	6 mo–14 yr	17–60 (37)	12 wk	Spontaneously reported
Nakken (2003) ³⁷ (n = 44)	Prospective, open-label	Add-on	Localization-related epilepsies and generalized epilepsies	3–17 yr	10–40	3–14 mo (8 mo)	Spontaneously reported
Aeby (2005) ³⁸ (n = 12)	Retrospective	Add-on (n = 11) and mono (n = 1)	Epilepsies and syndromes undetermined whether focal or generalized: with both generalized and focal seizures	4–14 yr	50	2 mo	Spontaneously reported
Lagae (2005) ²⁹ (n = 77)	Prospective, open-label	Add-on (n = 67) and mono (n = 10)	Localization-related epilepsies and generalized epilepsies	6 mo–16 yr	12–62 (mono: 29, add-on: 33)	20 wk	Structured questionnaire
Glauser (2006) ²⁷ (n = 198)	Randomized, double-blind, placebo-controlled	Add-on	Localization-related epilepsies	4–16 yr	40–60	14 wk	Spontaneously reported
Khurana (2007) ³⁹ (n = 18)	Retrospective	Mono	Localization-related epilepsies and generalized epilepsies	2.5–18 yr	14–60 (25)	2–24 mo	Spontaneously reported
Perry (2008) ⁴⁰ (n = 86)	Retrospective, LEV (n = 66) vs. CBZ (n = 20)	Mono	Localization-related epilepsies	<16 yr	Unknown	6 mo	Spontaneously reported
Verrotti (2008) ⁴¹ (n = 21)	Prospective, open-label	Mono	Generalized epilepsies	5–13 yr	31–70	6 mo	Structured questionnaire
Levisohn (2009) ²⁶ (n = 98)	Randomized, double-blind, placebo-controlled	Add-on	Localization-related epilepsies	4–16 yr	20–60 (53.6)	12 wk	Spontaneously reported
Pina-Garza (2010) ⁴² (n = 152)	Prospective, open-label	Add-on	Localization-related epilepsies	1 mo–<4 yr	10.5–95.4 (56.1)	30–42 wk (41 wk)	Spontaneously reported, structured questionnaire
Chhun (2011) ⁴³ (n = 102)	Prospective, open-label	Add-on	Localization-related epilepsies, generalized epilepsies and epilepsies and syndromes undetermined whether focal or generalized: with both generalized and focal seizures	6 mo–15 yr	25.0–44.8 (31.1)	6 mo	Structured questionnaire
Fattore (2011) ²⁸ (n = 59)	Randomized, double-blind, placebo-controlled	Mono	Generalized epilepsies	4–16 yr	10–30 (28.5)	14 dy	Spontaneously reported
Kanemura (2013) ⁴⁴ (n = 11)	Case series	Add-on	Localization-related epilepsies and epilepsies and syndromes undetermined whether focal or generalized: with both generalized and focal seizures	4.7–11.3 yr	19.4–57.7 (44.8)	6 mo	Spontaneously reported

n, number of patients included in study; LEV, levetiracetam; CBZ, carbamazepine.

^a Classification of epilepsies and syndromes according to ILAE 1989.

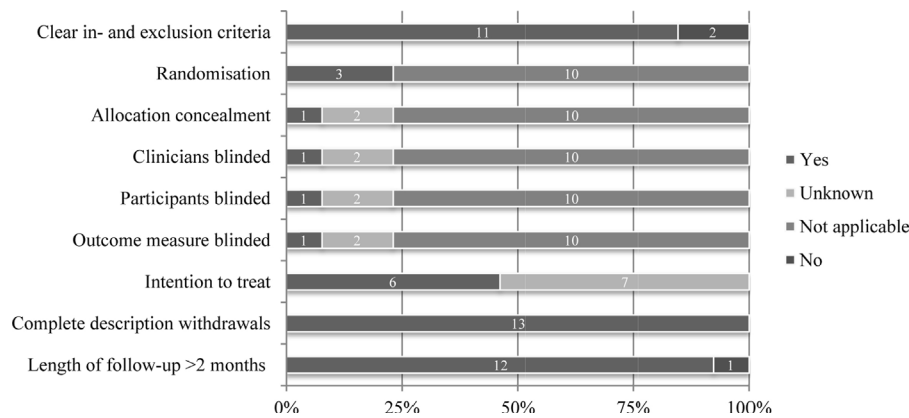


Fig. 2. Quality assessment of included studies.

received levetiracetam treatment, and so randomization and blinding were not applicable to these studies resulting in a high risk of information bias.^{29,36–39,41–44} The risk of selection bias was low in these studies since the inclusion and exclusion criteria were well-chosen and clearly described in seven out of nine studies.^{29,36,37,39,41–43} One study retrospectively compared levetiracetam and carbamazepine, but only the results of levetiracetam treatment were described here.⁴⁰ About half of studies (6/13) used an intention to treat analysis^{26–28,36,42,43} and all provided a complete description of withdrawals.^{26–29,36–44} Only one study had a follow-up duration of less than two months (fourteen days).²⁸

In conclusion, there is a large heterogeneity among the included studies with regard to study design, study population, intervention and outcome measures (Fig. 2). Ten studies did not include a control group and therefore a meta-analysis was not possible.^{29,36–44} The randomized controlled trials were not sufficiently homogeneous concerning specific behavioral side-effects. Therefore, we could only carry out a meta-analysis for the total number of behavioral side-effects from these studies.^{26–28} Because of the heterogeneity among the included studies and differences in levels of evidence, the results of the randomized controlled trials and the results of the observational studies will be described separately.

3.3. Evidence from randomized controlled trials

Three randomized controlled trials were included in this study.^{26–28} A total of 62 behavioral side-effects were reported in 203 patients with hostility (5.9%), nervousness

(4.9%) and aggression (3.9%) being reported mostly. One-hundred and sixty-five patients received levetiracetam add-on therapy and 59 behavioral side-effects were reported within this group (mostly hostility (7.3%), nervousness (6.1%) and aggression (4.9%)).^{26,27}

There is a statistically significant difference in the total number of behavioral side-effects between patients receiving levetiracetam and patients receiving placebo in the study of Glauser et al.²⁷ but this was not found in the study by Levisohn et al.²⁶ and Fattore et al.²⁸ No statistically significant differences were found between levetiracetam and placebo for specific behavioral side-effects with the exception of nervousness (Table 2). Overall, 62 behavioral side-effects in 203 patients using levetiracetam compared to 21 behavioral side-effects in 152 patients using placebo does show a trend of behavioral side-effects being more prevalent in patients using levetiracetam over placebo.

Fig. 3 shows the meta-analysis on total number of behavioral side-effects of levetiracetam versus placebo. This shows a statistically significant risk ratio of 2.18 [1.42, 3.37] for behavioral side-effects when using levetiracetam compared to placebo.

Two randomized controlled trials reported specific reasons for discontinuation of levetiracetam.^{26,28} In these 102 patients, only two patients (2.0%) stopped using levetiracetam because of behavioral side-effects (abnormal behavior/depression and agitation). In the study of Glauser et al. five of 101 patients discontinued levetiracetam because of side-effects but they did not clarify if behavioral side-effects were involved.²⁷

Table 2
Statistical tests of behavioral side-effects between levetiracetam and placebo.

Study	Outcome measure	Levetiracetam	Placebo	p value (test used)
Levisohn (2009)	Aggression	8/64	3/34	$p = 0.743$ (2-sided Fisher's exact)
	Abnormal behavior	5/64	0/34	$p = 0.160$ (2-sided Fisher's exact)
	Hyperactivity	4/64	5/34	$p = 0.269$ (2-sided Fisher's exact)
	Anxiety	4/64	0/34	$p = 0.295$ (2-sided Fisher's exact)
	Altered mood	4/64	0/34	$p = 0.295$ (2-sided Fisher's exact)
	Total no. of behavioral side-effects	25/64	8/34	$p = 0.121$ (Chi-square)
Glauser (2006)	Hostility	12/101	6/97	$p = 0.163$ (Chi-square)
	Nervousness	10/101	2/97	$p = 0.033$ (2-sided Fisher's exact)
	Emotional lability	6/101	4/97	$p = 0.748$ (2-sided Fisher's exact)
	Agitation	6/101	1/97	$p = 0.119$ (2-sided Fisher's exact)
	Total no. of behavioral side-effects	34/101	13/97	$p = 0.001$ (Chi-square)
Fattore (2011)	Irritability	2/38	0/21	$p = 0.534$ (2-sided Fisher's exact)
	Dysphoria	1/38	0/21	$p = 1.000$ (2-sided Fisher's exact)
	Total no. of behavioral side-effects	3/38	0/21	$p = 0.546$ (2-sided Fisher's exact)

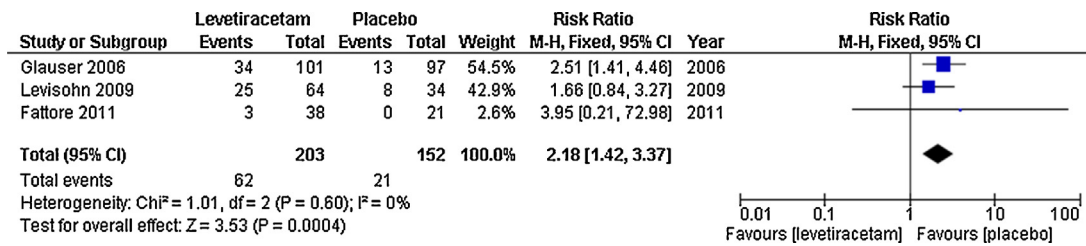


Fig. 3. Forest plot of total number of behavioral side-effects, levetiracetam versus placebo.

3.4. Evidence from observational studies

A total number of 89 behavioral side-effects were reported in 524 patients. Not all studies reported specific behavioral side-effects; five studies reported behavioral side-effects in general.^{36–40} Overall the most reported behavioral side-effects were behavioral problems in general (5.0%), irritability (4.2%), and hyperexcitability (3.4%). Additional behavioral side-effects which were reported were aggression (2.1%), agitation (1.2%), restlessness (1.0%) and psychosis (0.2%).

Seven studies, including 408 patients, used levetiracetam add-on therapy in localization-related or generalized epilepsies and reported a number of 64 behavioral side-effects.^{29,36–38,42–44} Irritability (4.7%), hyperexcitability (4.4%) and aggression (2.7%) were reported mostly within this group. Monotherapy was given in 116 patients with localization-related or generalized epilepsies.^{29,38–41} In this subgroup a total of 25 behavioral side-effects, consisting of behavioral problems in general (19.0%) and irritability (2.6%), were found.

Nine studies, including 422 patients, reported specific reasons for discontinuation of levetiracetam.^{29,36–42,44} Behavioral side-effects were a reason for discontinuation in eleven patients (2.6%). In one other study, five of 102 patients discontinued levetiracetam because of side-effects but they did not specify the different side-effects.⁴³

Three studies also reported possible improvements in behavior after starting levetiracetam. In seven of eleven patients, hyperactivity and impulsivity improved after levetiracetam treatment; these patients were all responders.⁴⁴ In the second study, seventeen of 77 patients showed better behavior, meaning it became easier to handle the children and introduce more structure in their behavior.²⁹ In the last study, seven of twelve patients showed improved behavior after two months of levetiracetam as reported by the parents and/or school; all these patients also showed an improvement on their electroencephalogram.³⁸

4. Discussion

The objective of this systematic review was to provide a better overview of the frequency and variety of behavioral side-effects of levetiracetam in children with epilepsy. We conducted a literature review of various behavioral side-effects most likely to be initiated by levetiracetam in children.

Most reported findings from randomized controlled trials were hostility, nervousness and aggression. We showed that behavioral side-effects are indeed frequently reported when using levetiracetam with a total number of 62 behavioral side-effects occurring in 203 patients. A statistically significant difference in the total number of behavioral side-effects between patients receiving levetiracetam versus placebo was found in only one randomized controlled trial. Also Chi-square and Fisher's exact tests showed no statistical significance for specific behavioral side-effects except for nervousness. A possible explanation might be the low number of patients included in the analyses for specific behavioral

side-effects. However, the meta-analysis did show a statistically significant risk ratio of 2.18 for levetiracetam versus placebo. These behavioral side-effects led to discontinuation of levetiracetam in only two of 102 patients (2.0%). This might be an underestimation since one other study reported discontinuation of levetiracetam due to side-effects in five patients which possibly include behavioral side-effects. On the other hand, Bertsche et al. analyzed therapy failure of levetiracetam and other AEDs and they also reported a low number of patients discontinuing levetiracetam because of side-effects; the majority of patients stopped levetiracetam because of lack of effectiveness.⁴⁵

The evidence from the observational studies showed mixed results with both behavioral deteriorations and improvements following levetiracetam. Epilepsy in children is associated with behavioral problems and a negative psychosocial impact.^{1,3} Improvements in behavior by levetiracetam may, therefore, be related to a better seizure control.² Behavioral improvements in the long-term may be explained by parents getting used to their child's behavior or because the dose of levetiracetam was flexible during a long-term, open label study.⁴² It would have been interesting to look at the timing of and influence of the dose on behavioral side-effects. Unfortunately only one observational study reported on the timing of behavioral side-effects and another about the influence of the dose of levetiracetam. Due to this lack of evidence we decided not to include these topics in our systematic review.

It is worth speculating about the clinical relevance of behavioral side-effects caused by levetiracetam since a very low number of patients discontinued levetiracetam in both randomized controlled trials and observational studies. This low number indicates that the behavioral side-effects are not that severe because otherwise probably more patients would have discontinued levetiracetam. Also Bootsma et al. assume that side-effects are only clinically meaningful when an AED is discontinued because of this side-effect.⁴⁶

The reported behavioral side-effects in the included studies are all of an activating-type; defined as 'uppers' by Ketter et al.³¹ This is not in line with previous studies of Roberts et al. and Bootsma et al. who found both activating and deactivating side-effects in patients using levetiracetam.^{32,46} Both children and adults who used levetiracetam were included in these studies; it might be possible that adults are more likely to develop deactivating side-effects compared to children.

Unfortunately, most studies (10/13) were neither randomized nor blinded and, therefore, are influenced by varying methodology, information bias and the validity of measuring behavioral side-effects since in most studies behavioral side-effects had to be reported spontaneously or were asked about by the investigator. This method is vulnerable to bias because parents are probably familiar with the possible side-effects of the medication and more likely to answer 'yes' to a specific question asked by the doctor. This may result in a possible overestimation of behavioral side-effects. The lack of randomized controlled trials concerning behavioral side-effects of levetiracetam in children may be explained by

ethical objections, as it is not ethically justified to give children medication in order to look for harmful side-effects.

As far as we know, this is the first systematic review on behavioral side-effects of levetiracetam in children with epilepsy. We have demonstrated a noteworthy frequency and variety of behavioral side-effects in children using levetiracetam but the severity of these behavioral side-effects is still a point of discussion. However, our results suggest that behavioral problems are more likely to occur or worsen in patients using levetiracetam compared to patients using placebo. Further research is needed to gain a better understanding of the relation between seizure control and deterioration or improvement in behavior. The severity and impact of the behavioral side-effects caused by levetiracetam in children should also be investigated. Based on the findings in this systematic review, children using levetiracetam have a risk of developing several behavioral side-effects such as aggression, hostility and nervousness compared to children who do not use levetiracetam.

Conflicts of interest

None of the authors has any conflict of interest to disclose. We affirm that this report is consistent with the guidelines on issues involved in ethical publication of Seizure.

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Appendix A. Search strategy PubMed

- (infant[Mesh] OR infant OR infants) OR (baby OR babies) OR (neonate OR neonates OR neonatal) OR (perinate OR perinates OR perinatal) OR (postnatal OR postnates) OR (child[Mesh] OR child OR children) OR (schoolchild OR schoolchildren) OR (kid OR kids) OR (toddler OR toddlers) OR (adolescent[Mesh] OR adolescent OR adolescents OR teen OR teens) OR (boy OR boys OR girl OR girls) OR (minors OR underage OR underaged OR "under aged") OR (juvenile OR juveniles OR youth) OR (puberty[Mesh] OR puberty OR puber OR puberal OR prepuberty) OR (pediatrics[Mesh] OR pediatrics OR pediatric OR paediatric OR paediatric OR paediatrics OR paediatric) OR (schools[Mesh] OR schools OR school OR "nursery school" OR "nursery schools") OR (preschool OR "pre school" OR "pre schools" OR "primary school" OR "primary schools") OR ("secondary school" OR "secondary schools") OR ("elementary school" OR "elementary schools") OR ("high school" OR "high schools" OR highschool OR highschools) OR ("school age" OR "school ages")
- (etiracetam[Supplementary Concept] OR Levetiracetam OR Keppra OR Etiracetam)
- (epilepsy[MeSH] OR epilepsy OR epileps* OR epilept*) OR (seizures[MeSH] OR seizures OR seizure) OR (convulsion OR convulsions)
- "behavior"[MeSH Terms] OR "behavior*" OR "behavior*" OR "Mood Disorders"[Mesh] OR "Mood disorder" OR "Mood disorders" OR "Affective disorder" OR "Affective disorders" OR "aggression" OR "Aggression"[Mesh] OR "agression" OR "agressive" OR "irritability" OR "Irritable Mood"[Mesh] OR "irritable" OR "Psychomotor Agitation"[Mesh] OR "Agitation" OR "Agitated" OR "Agitate" OR "Hyperactivity" OR "Hyperactive" OR "Restlessness" OR "Restless" OR "Impulsive Behavior"[Mesh] OR "Impulsive" OR "Impulsiveness" OR "Hostility"[Mesh] OR "Hostility" OR "Hostile" OR "Nervousness"

- Limits: Humans, Dutch, English, German, Child: birth–18 years, Infant: birth–23 months, Adolescent: 13–18 years, Child: 6–12 years, Infant: 1–23 months, Preschool Child: 2–5 years, Journal Article.

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