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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.

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

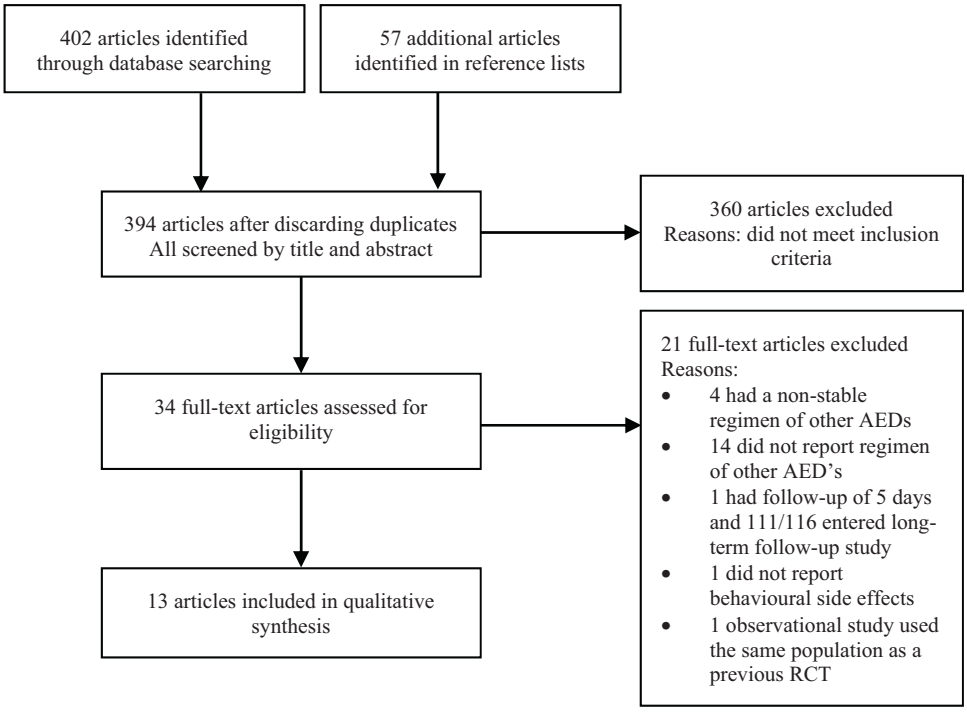

Fig. 1. Flow-diagram of study identification and selection.