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REVIEW

RCTs with new antiepileptic drugs in children: A systematic review of monotherapy studies and their methodology

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Summary Few randomised controlled trials (RCTs) have been performed in which a second-generation antiepileptic drug (AED) used as monotherapy was compared with placebo or another AED in children (<18 years of age) with epilepsy. We describe the results of the available studies, assess the validity of these results, and give recommendations for optimal study design for AED monotherapy studies in children with epilepsy.

Studies were identified using PubMed (Medline), Embase and the Cochrane Library (January 1990—January 2010). All reports were assessed for methodological quality and results were summarised descriptively.

Nine RCTs were included. No difference in efficacy and safety between second-generation AEDs and first-generation AEDs in children was detected. Considerable heterogeneity in study design, inclusion criteria and primary endpoints impaired formal meta-analysis and correct interpretation of results. Follow-up periods were between 2 and 104 weeks; the dosage of the tested AEDs varied between studies, with sometimes use of apparent subtherapeutic dosages; in only two studies the method of randomisation was well described, in only three the power calculations; several studies did not use an intention-to-treat analysis. Although from the available studies first- and second-generation AEDs appear to have similar efficacy and safety in children with epilepsy, these trials are inadequate to provide a sufficient evidence base for decision making. Better trials are needed: AEDs should be studied in optimal

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paediatric doses, power should be sufficient to detect small but clinically relevant differences, and the follow-up period should be long enough. Most important, primary endpoint to be evaluated should be time to treatment failure or retention rate, since these outcomes combine efficacy and safety.

Contents

Introduction

In children with epilepsy, psychomotor development may be negatively influenced by persistent seizure activity and side effects of the anti-epileptic medication. Good seizure control with no or minimal side effects is the desired endpoint for these children and their families. In some children, first-generation anti-epileptic drugs (AEDs) are insufficient to control seizures or drug-related adverse events may lead to discontinuation of these AEDs. Second-generation AEDs may be more effective and may yield fewer side effects.

In the last 15 years, seven second-generation AEDs have been licensed as add-on therapy for children (Table 1). Six of these have also been licensed as monotherapy: vigabatrin, topiramate, lamotrigine, oxcarbazepine, levetiracetam (only in children over 16 years of age) and gabapentin. Monotherapy treatment is preferred over polytherapy because interactions with other AEDs are not present, and fewer drug-induced adverse events occur, which will improve compliance. Yet, only a few studies have been performed in children with epilepsy comparing the effects of second-generation AEDs used as monotherapy with placebo or other AEDs (both first- and second-generation) (Trudeau et al., 1996; Guerreiro et al., 1997; Bourgeois et al., 1998; Frank et al., 1999; Nieto-Barrera et al., 2001; Coppola et al., 2004, 2007; Wheless et al., 2004; Resendiz-Aparicio et al., 2004). Most studies on efficacy and safety of second-generation drugs have been performed in adults. The response to AEDs may vary between children and adults due to, for instance, different pharmacokinetics (Dulac, 2005). Also, both the severity and incidence of adverse events may be different in adults and children. Furthermore, there is a wide range of epilepsy syndromes that mainly occur in children, some of them being rather benign, others, like West and Lennox-Gastaut syndrome, having a generally unfavourable prognosis.

The most recent systematic review on second-generation AEDs in children with epilepsy mainly included studies in which AEDs were given as add-on therapy and studies in which second-generation AEDs were not compared with other AEDs (Chung and Eiland, 2008). We performed a systematic review in which we describe the results of randomised controlled studies comparing the effects of second-generation AEDs used as monotherapy with placebo or other AEDs and relate these results to the methodological and clinical validity of the trials. Also based on the findings of this review, we give some recommendations for an optimal study design for AED monotherapy studies in children with epilepsy.

Methods

We included all identified studies in children (<18 years of age) with epilepsy in which any of the following second-generation AEDs used as monotherapy were compared with placebo or other AEDs: oxcarbazepine, felbamate, lamotrigine, gabapentin, levetiracetam, pregabalin, zonisamide, topiramate, and tiagabine. Vigabatrin has only been registered as monotherapy for West syndrome and has limited use in other epilepsies due to its irreversible side effect of visual loss. Therefore, it was not included in this review. Studies were identified using PubMed (Medline), Embase and the Cochrane Library (from January 1990 until January 2010). The following search terms were used: 'epilepsy AND child* AND monotherapy AND (oxcarbazepine OR felbamate OR lamotrigine OR gabapentin OR levetiracetam OR pregabalin OR zonisamide OR topiramate OR tiagabine)' with the limitation: Randomised Controlled Trials (RCT). The obtained studies were used to search for further references. References in English, German, French, Spanish, Italian, and Dutch were included.

If a study included both children and adults, it was reviewed only if the results of efficacy and safety were reported separately for children. Of these studies only the data concerning children are described and discussed. All reports were assessed for study design and methodological quality for which we evaluated the method of randomisation concealment, duration of treatment and follow-up, attrition and whether children had been excluded from the analyses. We abstracted clinical characteristics of participants and data on seizure-freedom, retention rate, time to treatment failure, >50% seizure-reduction, and reported adverse events. The data were independently extracted from the trial reports by two authors (AW and PC). If retention rate was not given in the article, it was calculated by us. Since this systemic review includes reports on a series of AEDs evaluated in children with various different epilepsy syndromes,