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FULL-LENGTH ORIGINAL RESEARCH

Investigator-initiated randomized controlled trials in children with epilepsy: Mission impossible?

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Summary

Objective: **In children many antiepileptic drugs (AEDs) are prescribed off-label due to a lack of well-designed randomized controlled trials (RCTs). We conducted a multicenter RCT in the Netherlands to compare levetiracetam and valproic acid as monotherapy in children with newly diagnosed epilepsy. After 2 years, we had to stop this investigator-initiated trial prematurely because the inclusion rate was too low. We analyzed the reasons for this failure, assessed the various issues involved in performing RCTs in children, and now give recommendations for future studies.**

Methods: **A questionnaire was completed by all investigators involved in the study. It included questions about the motivation to participate and the perceived reasons for recruitment failure. We also studied literature about financial, logistic, legal, and ethical aspects of RCTs in children.**

Results: **Main reasons for recruitment failure were overestimation of the number of eligible AED-naive children referred by general pediatricians; personal preferences of investigators for specific antiepileptic drugs; and the extensive administrative load due to extra regulations and guidelines for children. Fundraising for investigator-initiated trials is difficult and the majority of RCTs concerning AEDs are sponsored by pharmaceutical companies. Involving children requires balancing between protection and participation; the randomization procedure and obtaining informed consent are complex for both children and parents.**

Significance: **Performing RCTs with AEDs in children is important but complicated by logistic, regulatory, legal, and ethical restrictions. Based on our recent experience, our advice to colleagues who are planning a similar trial would be to perform a feasibility pilot study; to set up intensive collaboration with referring pediatricians; to arrange support of a clinical trials unit and a local research nurse during the complete trial period; and to incorporate the possibility of extending the recruitment period. Major investments, both financially from governmental organizations and in time, are imperative for independent RCTs in children.**

KEY WORDS: **Antiepileptic drugs, Off-label, Feasibility.**

Epilepsy is one of the most common neurological disorders in childhood, with an estimated incidence of 82/100,000 children per year.[1] Seizures are most commonly treated with antiepileptic drugs (AEDs). During the last 25 years, the number of available AEDs has increased considerably.[2] Few of the newer AEDs are licensed for monotherapy use in children, such as lamotrigine, oxcarbazepine and topiramate, but the majority are still prescribed off-label. For several reasons, efficacy and tolerability of new AEDs need to be tested in children separately.[3,4] Recently, the International League Against

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[1]LEV-VPA Study Group members' details are presented in Appendix 1.

Key Points

- RCTs in children with epilepsy are scarce, and prescribing medication off-label based on personal treatment preferences is generally accepted
- Performing RCTs in children is challenging, with important financial, logistic, regulatory, legal, and ethical aspects
- For independent RCTs in children, major investments, both financially from governmental organizations and in time, are imperative

Epilepsy concluded that there is a lack of well-designed, properly conducted randomized controlled trials (RCTs) concerning initial monotherapy for epilepsy, especially in children.[5] It proposed an ideal design for such RCTs, with either effectiveness (patient retention) or efficacy (seizure freedom) as primary endpoint, a minimum of 48 weeks of treatment for all seizure types, double-blind design, and use of an acceptable comparator.[5,6]

We recently conducted a multicenter RCT in the Netherlands to compare levetiracetam (LEV) and valproic acid (VPA) as monotherapy in children with newly diagnosed epilepsy (LEV-VPA Study, NTR3784). We aimed to provide the highest level of evidence (level A) for LEV monotherapy in children instead of the current level D evidence.[5,7] Unfortunately, we had to stop the trial prematurely because the recruitment rate was too low.

To learn from this experience and to help others prevent a similar disappointment, we critically analyzed the reasons for the failure of our trial. We also assessed the various issues involved in performing these clinical trials, including financial, logistic, legal, and ethical aspects. Finally, we give some recommendations to those colleagues who are planning an RCT in children.

LEV-VPA Study

The aim of this double-blind, multicenter trial was to investigate the efficacy, safety, and tolerability of LEV monotherapy versus VPA monotherapy as first-line treatment in children aged 4–16 years with newly diagnosed epilepsy in the Netherlands. Nine pediatric neurologists from four academic centers and five general hospitals participated, covering an estimated referral area of 70% of the total Dutch pediatric population of almost 2 million children aged 5–15 years. We calculated approximately 1,150 children with newly diagnosed epilepsy might be identified as possible candidates for our study each year. Potential recruitment was based on the experience with the Dutch Study of Epilepsy in Childhood (DSEC), in which 350 children aged 4–16 years with newly diagnosed epilepsy were included in 4 years in four hospitals.[8] On the basis of these figures, it should be possible to recruit 200 children within 2 years. We visited regional hospitals and informed pediatricians about the study. After explanation of the trial, we asked them to participate by referring eligible children promptly to one of the nine participating centers without starting treatment. After informed consent, children were randomized for double-blind treatment with LEV (15–60 mg/kg/day) or VPA (10–40 mg/kg/day) monotherapy if they had had at least two seizures in the last 4 weeks before enrollment without having received any previous antiepileptic treatment for their seizures except for emergency medication. Because of the variation in body weight, capsules with five different dosages had to be produced to allow slow increases in dosage and to prevent children having to swallow a large number of capsules per day. The appropriate dosage of medication was transported to the individual centers directly after randomization. Children were treated for a maximum of 52 weeks with trial medication. Neuropsychological questionnaires and assessments were performed at the start and during the trial. Primary endpoint was retention rate after 52 weeks of treatment.

According to our power analysis for a noninferiority survival type trial, we calculated a needed sample size of 196 children to achieve 80% power to detect a noninferiority margin difference between the group proportions of −0.1600 (based on recommendations of the International League Against Epilepsy [ILAE] for noninferiority trials), assuming the retention rate for VPA to be 0.8000 (one-sided Z test [pooled], $p = 0.0253$).[6] Funding for this investigator-initiated trial was obtained from the Netherlands Organisation for Health Research and Development (ZonMW).

During a pretrial period of 3 years, the following tasks were completed: the protocol was written and approved by all participating investigators; funding was obtained; regional hospitals were visited, informed, and asked to participate; trial medication was manufactured; logistics concerning randomization, trial procedures, and electronic case report (eCRF) design were effectuated; and approval from ethical committees and boards of directors was obtained. The trial started in February 2013, but, because of administrative procedures, it took until December 2013 before the last center had permission to start inclusion. At the end of 2013, we had included only 4 children instead of the planned-for 100. To improve the inclusion rate, we amended our inclusion criteria: the youngest age of inclusion was lowered from 4 to 2 years, a minimal seizure frequency before entry was no longer required, and previous treatment with AEDs other than LEV or VPA was allowed, provided this had been withdrawn at least 1 year before inclusion. An extra year of inclusion was anticipated, but despite these adjusted inclusion criteria, the inclusion rate remained too low. In July 2014, 18 months after the start of the study, we had included 15 children with only five of the nine participating hospitals having been able to include at least one patient. We then decided to stop the trial.

Evaluation of the LEV-VPA study

Because of the disappointing premature discontinuation of the trial, we determined that the trial needed to be systematically evaluated. A questionnaire was sent out and returned by all nine investigators (see Appendix S1). It included questions about the motivation to participate and the perceived reasons for recruitment failure. One investigator could not include any patient because of personal circumstances and did not fully complete the questionnaire.

The most important motivation of the investigators to participate had been the lack of sound evidence of efficacy and safety of LEV in children and the fact that they still had to prescribe LEV monotherapy off-label because this drug is only registered as add-on treatment in children. They hoped that the results of this trial justified prescription of LEV as monotherapy and that, as a consequence, it could be registered for monotherapy in children.

The investigators gave several reasons for the low number of inclusions and failure of our trial. Most important was the extensive administrative load, e.g., getting approval of the board of directors for each hospital, obtaining written informed consent from both parents, handling emails from the trial coordinator and monitor, as well as having to complete a detailed eCRF and to follow many trial procedures. The heavy paperwork even withheld three centers from including any patient. Most investigators were convinced that more administrative support, for instance, from a research nurse, would have increased inclusion rate. This could have been achieved by financial support for every participating center to guarantee enough assistance.

Table 1 shows the other reasons for the low number of inclusion. The first reason was the investigator clinicians' preference for another AED in individual cases. One investigator wished to avoid prescribing VPA in girls (of any age); another investigator did not want to include children with childhood absences following the US RCT by Glauser et al.[9] that showed ethosuximide to be superior to valproate and lamotrigin. The results of this study were published during the grant application procedure of the LEV-VPA study, and no adaptations were made in our study protocol after publication of this trial. Nevertheless, every treating physician always kept the possibility not to include a patient because of personal preference for a specific treatment. However, we underestimated the influence of these personal preferences. A second common reason was refusal of parents to participate, for example, because they wanted to know which AED their child would receive before randomization. Training in communication about shared decision making with parents and children might have helped the investigators.[10] Another reason was an explosive seizure onset in some children that did not allow waiting for written informed consent and subsequent arrival of trial medication. The difficulty of including children requiring very urgent treatment might have been prevented by storage of study medication in each participating center but would have created higher storage costs. Moreover, because of the capsules with five different dosages and an unknown number of patients of each weight category to be included per participating center beforehand, an overload of study medication should have been produced, with a subsequent waste. Despite the amended inclusion criteria, the number of eligible children remained too low. On the basis of the figures of the DSEC, we had considered recruitment of 200 children to be possible within 2 years in our nine centers in close cooperation with pediatricians of regional hospitals.[8] However, our study was not an observational study like the DSEC, which was performed in the nineties of the last century, when commitment to participate in studies seemed to be higher. Furthermore, during the DSEC, most children were directly seen by pediatric neurologists, whereas nowadays they will generally first visit a local pediatrician. Our attempts to persuade regional pediatricians to refer children with newly diagnosed untreated epilepsy to one of the nine participating centers appeared to be in vain. In many cases these colleagues had already started medication before getting in touch with us. Logistically and financially (e.g., extra monitoring, participation of more pharmacies), it was not possible to carry out our multicenter trial in more than nine centers. Performing a feasibility study beforehand would probably have given a better indication of the expected recruitment rate in our trial.

Table 1. Reasons for not being able to include children, as given by eight investigators

	Frequency[a] (%)
Doctor's preference for a specific antiepileptic drug	5 (62)
Child/parents refused to participate	4 (50)
Too few children meeting inclusion criteria	4 (50)
Urgent antiepileptic treatment was required	2 (25)
Child became (spontaneously) seizure free (without treatment)	1 (12)

[a]Number of investigators giving this reason.

RCTs in Children with Epilepsy

Few well-executed RCTs comparing old and/or new AEDs in children with epilepsy have been performed,[11] and only two of them contributed level A evidence.[5,9,12] Results of AED trials performed in adults are often extrapolated to children. Extrapolation may be justified for add-on therapy in children from 2 to 18 years with focal seizures.[13] However, specific research in children is necessary because of the various seizure types and many different epilepsy syndromes that occur only in childhood and the differences in pharmacokinetics and pharmacodynamics in children and in adults.[11,13] The importance of RCTs in children has been well recognized and has led to the Paediatric Regulation in

the European Union in 2007[14] as well as initiatives such as the European Network of Paediatric Research (Enpr-EMA),[15] Priority Medicines for Children (PrioMedChild),[16] and StaR Child Health.[17] These networks aim to increase availability of registered drugs for children, with development of guidelines for clinical trials in children, as well as facilitating collaborations and supporting such studies financially. Performing an RCT in children, however, is challenging and several issues need to be addressed.[18,19]

Financial aspects

All currently published relevant RCTs concerning AEDs that have been performed in children with epilepsy were partially or fully sponsored by pharmaceutical companies. The primary goal of these trials was AED registration, and most of these were performed in adults with additional inclusion of a few children. Pharmaceutical companies have no financial incentive to carry out trials with any drug for which the patent has expired or is about to expire or to perform trials for a relatively small market, such as children with epilepsy. Fortunately, nowadays the Paediatric Regulation requires that all applications for marketing authorization of new medicines include the results of studies performed in children, as described in an agreed pediatric investigation plan. The only exception to this rule is when the medicine is likely to be ineffective, inappropriate, or unsafe for children.[14] If registration is extended to children, the patent will be prolonged for 6 months.

In contrast to research by pharmaceutical companies, investigator-initiated research depends on availability of funding. Only 4 of the 28 monotherapy trials in children with epilepsy recorded in Trial Registers (ClinicalTrials.gov, ISRCTN.com, or clinicaltrialsregister.eu) are investigator-initiated, one of them being our LEV-VPA trial (Table 2). Two studies are funded by the National Institute for Health Research (United Kingdom), and one by the Dutch National Epilepsy Fund (NEF) in cooperation with the Wilhelmina Research Fund (WKZ Fund) (the Netherlands). These three investigator-initiated trials are still recruiting. The other registered trials are all sponsored by pharmaceutical companies. One of these trials was prematurely stopped because the recruitment rate was too low, 18 trials have been completed, and 5 trials are ongoing. The results of only 6 of the 18 successfully completed trials have been published,[20–25] and results of another 3 trials have been described on ClinicalTrials.gov, but are not (yet) published.

To support studies in children in both Europe and the United States, special programs are offered. Studies in children require the same adequate infrastructure as RCTs in adults. Costs for RCTs in children are, therefore, at least as high, if not higher, compared to those in adults.[26] These extra costs are mainly caused by the large range of body weights and age categories. In our LEV-VPA study, we had to use different tests and questionnaires for neuropsychological assessments in children of many different age groups. Because of the capsules with five different dosages, the appropriate medication could only be transported to the individual centers after randomization, leading to more costs for production and distribution. More than 13% of our budget was spent on development and production of trial medication and a similar percentage on distribution. An alternative for these investigator-carried costs could be that pharmaceutical companies provide trial medication free of charge, as was done in the successful trial of Glauser et al.[9] Our total trial budget was €711,050 for 200 children, which means €3,555 per randomized child. The EcLiPSE study group (Emergency Treatment with Levetiracetam or Phenytoin in Status Epilepticus in Children; www.eclipse-study.org.uk), an investigator-initiated, 3-year, randomized open-label trial on LEV versus phenytoin monotherapy in status epilepticus in children, is funded by the National Institute for Health Research. It aims to include 308 patients in 25 centers, with a total budget of £1,515,580, which means approximately €7,000 per child. These amounts for

Table 2. Four investigator-initiated monotherapy trials in children with epilepsy found in Trial Registers

Study acronym	Funding	AED	Age category	Seizure type/ syndrome	Number of patients	Duration of the study treatment (duration of inclusion)
LEV-VPA	ZonMW	LEV vs. VPA	2–16 years	All	200	1 year (2 years)
SANAD II	NIHR	A. LEV vs. LTG vs. ZNS B. LEV vs. VPA	≥5 years	A. Focal B. Generalized or unclassified	A. 990 B. 520	2 years (3.5 years)
EcLiPSE	NIHR	LEV i.v. vs. PHT i.v.	6 months–18 years	Status epilepticus	308	14 days (3 years)
Rescue ESES	NEF + WKZ fund	Steroids vs. CLB	2–12 years	ESES + cognitive deficit	130	6 months (47 months)

AED, antiepileptic drug; CLB, clobazam; EcLiPSE, Emergency Treatment with Levetiracetam or Phenytoin in Status Epilepticus in Children; ESES, electrical status epilepticus in sleep; i.v., intravenous; LEV, levetiracetam; LEV-VPA, double-blind randomized trial comparing efficacy, safety, and tolerance between levetiracetam monotherapy and valproic acid monotherapy in children with newly diagnosed epilepsy; LTG, lamotrigine; NEF, Dutch National Epilepsy Fund; NIHR, National Institute for Health Research; PHT, phenytoin; Rescue ESES, Randomized European Trial of Steroids vs. Clobazam Usage for Encephalopathy with ESES; SANAD II, a comparison of Standard and New Antiepileptic Drugs; vs., versus; VPA, valproic acid; WKZ Fund, Wilhelmina Research Fund; ZonMW, Netherlands Organisation for Health Research and Development; ZNS, zonisamide.

investigator-initiated trials seem small compared to the budgets spent by pharmaceutical companies, for whom €100,000 per randomized child is rather rule than exception.

Logistics and recruitment

Performing a trial according to good clinical practice guidelines implicates an extensive and strict administrative load for each investigator. RCTs in children are even more complicated and time-consuming than those in adults because of extra regulations and body-weight-based medication. Help of research nurses in participating centers and support by a trial coordinator and clinical trials unit are therefore essential. Realistic calculation of the number of patients who can be included is one of the most important issues of every trial. A feasibility study is the best way to overcome recruitment problems. Recently, an industry-sponsored study had to stop prematurely because the inclusion rate was too low (44 instead of 120 patients in 18 months), and the limited trial budget did not allow extension.[27] In two successful monotherapy trials that provided level A evidence, the recruitment period was 51 (initially unknown) and 40 (initially planned 36) months, respectively.[9,12] Although details on planned and real duration of the inclusion period are not known, in many trials start of recruitment was delayed and period of recruitment had to be extended. Because of these known recruitment issues, the inclusion period should be longer than expected beforehand.

Specifically in monotherapy studies, children with newly diagnosed epilepsy must be included before initiation of treatment. These children are most often primarily seen by a general pediatrician instead of a pediatric neurologist. To be able to include a sufficient number of AED-naive children, we therefore tried to increase the awareness of this study and involve general pediatricians of regional hospitals before the start of the study. Unfortunately, this did not result in many referrals. This is probably the most important reason of failure of our study.

In addition, the investigators, all experienced specialized pediatric neurologists, often had different personal preferences for a certain AED instead of randomizing children for trial medication. Although we knew some of these preferences beforehand, we underestimated their influence. Prescribing medication off-label based on personal treatment choices seems to be rather easily accepted as routine care, and the need to persuade doctors, children, and their parents to participate in trials seems limited.[28]

Legal and ethical considerations

Nowadays it is accepted that children participate in RCTs, but it is difficult to keep a good balance between protection and access, and to meet all the bureaucratic conditions.[18] If children are involved in epilepsy research, the research should be of high quality with an adequate sample size. RCTs including mainly adults but also children should at least describe the results for these children separately, which is not always the case.[29] Placebo-controlled trials are undesirable because of ethical limitations, and children with drug-resistant focal epilepsy have been reported to show a greater response to placebo compared to adults.[3,30] A children's research network in which multidisciplinary, cross-institutional groups are formed of (non)clinical child health researchers with access to diagnostic and laboratory facilities suitable for children, encouraging children and families to work closely with researchers in a so-called partnership forum, could be an ideal way for collecting data and focusing on specific issues.[31]

The randomization procedure itself is generally poorly understood by parents,[32] or they think that doctors already know which treatment is better. Even in our trial, with two established first-choice AEDs, randomization was one of the reasons for parents to refuse participation. Obtaining informed consent is also an issue because in the Netherlands both parents need to give permission, and from 12 years of age the child must sign as well.[33] As shown in the Informed Consent and Assent Tool kit, differences between national consent procedures exist in Europe.[34] Especially for international studies, a uniform guideline is desirable.

Conclusion

The design of the LEV-VPA study corresponded to the proposed design of the ILAE for a noninferiority RCT in children with an acceptable comparator and a sample size large enough to show noninferiority with a ≤20% relative difference between treatment arms.[6] Despite the sound methodological design and a motivated group of experienced investigators, our trial still had to end prematurely. The intended collaboration with regional pediatricians did not succeed, and we were not able to recruit enough children. Other important aspects that played a role were the personal preferences of the doctors and the extensive administrative load.

Although the ILAE recognizes problems in performing RCTs in children, they do not give recommendations on how to realize more successful trials in children.[5,6] Despite differences in national guidelines and governance requirements, most encountered problems when performing RCTs in children are not country specific. The chance of success could be increased by: (1) a feasibility pilot study; (2) better prepared and more intensive collaboration with referring regional pediatricians; (3) support of a clinical trials unit during the complete trial period; (4) local support of a well-trained research nurse in every participating center to handle the administrative load during both the pretrial and the trial phases as well as to support recruiting children; (5) a longer recruitment period. Consequently, major investments, both financially and in time, are necessary.

But who is willing to pay for this? To date, none of the successful RCTs on monotherapy in children with epilepsy has been completely funded by noncommercial funding organizations. Also, the ILAE recognized that many trials are designed, conducted, and analyzed by pharmaceutical companies and not by independent, unbiased sponsors.[6] Are investigator-initiated RCTs in children with epilepsy not feasible and should we accept off-label prescription for children with epilepsy guided by personal treatment preference? Together with the various initiatives to promote trials in children, we as clinical investigators should make this mission possible. For these independent trials major investments from governmental funding organizations are imperative. We hope higher budgets made available for investigator-initiated RCTs, such as the grants from the National Institute for Health Research for the EcLiPSE study and SANAD II trial, will become the rule rather than the exception.

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Disclosure

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Appendix I

LEV-VPA Study Group

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Questionnaire on the feasibility of the LEV-VPA study.