Childhood Absence Epilepsy—A Review of Treatment Strategies and Perspectives for the Future

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Abstract
Childhood absence epilepsy (CAE) is one of the most common forms of pediatric epilepsy. However, there is still a gap between the prevalence of CAE in pediatric epilepsies and the paucity of available data regarding its therapeutic management. Only nine randomized controlled trials have been published in the field over the past four decades, with many suffering from major methodologic limitations. A recent large randomized double-blind controlled trial reported that ethosuximide and sodium valproate are the most effective anti-epileptic drugs in CAE and that cognitive performance appears to be better with ethosuximide than with sodium valproate. Although lamotrigine also demonstrated anti-absence properties in the same trial, it proved to be significantly less efficacious than ethosuximide or sodium valproate. Despite these recent advances, several questions, including long-term outcomes, management of refractory CAE and treatment duration, remain unanswered and further studies are required to refine therapeutic decisions.

Keywords
Childhood absence epilepsy, anti-epileptic drug

What do Anti-epileptic Drug Trials Show?
Despite the increasing number of AEDs that have been licensed for the treatment of seizure disorders over the past 20 years, only a few have been evaluated in the treatment of CAE. Consequently, valproic acid (VPA) and ethosuximide (ESM) have been used as first-line agents for the treatment of absence seizures for over 40 years. Over these four decades, only nine randomized controlled trials (RCTs) have been published in the field, with many suffering from major methodologic limitations. RCTs are separated into four classes according to the rating scale of their level-of-evidence, with the highest being class I. To be classified as class I or II, monotherapy AED trials should fulfill:

- a double-blind randomized controlled design;
- efficacy as primary outcome;
- a treatment duration ≥24 weeks;
- a sufficient sample size to show non-inferiority of no worse than a 20 % relative difference in efficacy;
- study exit not forced by a predetermined number of treatment-emergent seizures; and
- an appropriate statistical analysis.

Based on this rating scale, the level of evidence for each AED can be determined, with the highest value (level A and B) implying that...
at least one class I and/or II study is available. Furthermore, quality assessment of RCTs in CAE should also consider the clinical relevance of the primary efficacy endpoint. Indeed, patients with CAE can demonstrate both electro-clinical absence seizures and isolated generalized spike and wave bursts on EEG without clinically detectable absences. Importantly, cognition might be impaired during so-called infra-clinical absences and clinicians often face the issue as to whether they should revise treatment when such EEG discharges persist while clinically detectable absences are fully controlled. In this context, RCTs should assess the disappearance of both spontaneous and hyperventilation-triggered EEG discharges.

Most of the studies that evaluated AEDs in CAE did not fulfill the quality criteria required to be classified as a class I or II study. Indeed, until 2010, all available RCTs were classified as class III studies according either to open-label design (n=4) or to inadequate treatment duration despite double-blind design (n=4).

Among the four open-label studies, two of the studies compared VPA and ESM10,15 and the other two studies compared VPA and LTG11 (see Table 1). Patients were between four and fifteen years old. Sample sizes were limited, comprising between 20 and 38 patients and the duration of the follow-up ranged from 12 months to four years. No difference was observed between VPA and ESM: the seizure-free rate ranged from 40.0 to 70.0 % with VPA compared with 57.1 to 80.0 % with ESM. Similarly, the two studies that compared VPA and LTG showed similar seizure-free rates with either drug. At the one-year follow-up, between 52.6 and 66.6 % of patients were controlled by LTG compared with between 68.4 and 80.0 % with VPA. However, these two latter studies also suggested that VPA efficacy was faster than that of LTG. Indeed, at one month, 52.6 to 60.0 % of patients treated with VPA were seizure-free compared with 0.0 to 5.3 % of patients treated with LTG; whereas at three months, seizure freedom was observed in 63.1 to 73.3 % of patients taking VPA versus 38.6 to 53.3 % taking LTG. Even at one year, the non-significant differences observed between drugs exceeded a relative difference of 20 %, suggesting that an adequate sample size would have resulted in showing statistically and clinically relevant superiority of VPA over LTG.

Among the four short-term double-blind controlled studies, one study compared VPA and ESM9 and the other three studies were placebo-controlled trials that compared either gabapentin (GBP),17 LTG13 or levetiracetam (LEV)12 with placebo (see Table 2).

Sato and colleagues compared VPA and ESM in a randomised double-blind response-conditional crossover study.16 Sixteen naive and 29 drug-resistant patients aged three to 18 years with absence seizures were included. They received either VPA with placebo for six weeks followed by ESM with placebo for six weeks or the same regimen in the reverse order. However, patients who were responders during the first treatment period were not crossed over to the alternative treatment. At the end of the first period of the crossover, there was a trend toward a non-significant higher seizure-free rate with VPA (40.9 %) than with ESM (34.8 %). However, when both treatment periods were included in the analysis, the probability of response to VPA was 37.3 ± 3.5 versus 38.3 ± 3.4 % to ESM.
Table 2: Short-term Double-blind Controlled Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial Characteristics</th>
<th>Epileptic Syndrome</th>
<th>Age (Years)</th>
<th>Inclusion Criteria</th>
<th>Event</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Seizure-free Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sato et al., 1982</td>
<td>Group 1 Group 2</td>
<td>ESM VPA</td>
<td>16 23</td>
<td>Drug-naïve and drug-resistant</td>
<td>Response-conditional</td>
<td>34.8</td>
<td>40.1*</td>
<td>3.8</td>
</tr>
<tr>
<td>Trudeau et al., 1996</td>
<td>Group 1 Group 2</td>
<td>GBP PCB</td>
<td>17 15</td>
<td>Newly diagnosed CAE</td>
<td>Parallel group</td>
<td>6.7</td>
<td>22.2</td>
<td></td>
</tr>
<tr>
<td>Frank et al., 1999</td>
<td>Group 1 Group 2</td>
<td>LTG PCB</td>
<td>13 15</td>
<td>Newly diagnosed typical absence seizures</td>
<td>'Responder-enriched' study design</td>
<td>62.0</td>
<td>21.0</td>
<td></td>
</tr>
<tr>
<td>Fattore et al., 2011</td>
<td>Group 1 Group 2</td>
<td>LEV PCB</td>
<td>12 38</td>
<td>Newly diagnosed CAE</td>
<td>Parallel group</td>
<td>23.7</td>
<td>4.8</td>
<td></td>
</tr>
</tbody>
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PCB = placebo; VPA = sodium valproate.

GBP was compared with placebo during a two-week double-blind trial in newly diagnosed CAE. Sixteen patients were randomly allocated to placebo and 15 to GBP. At the end of the double-blind period, four patients were responders in the placebo group compared with only one in the GBP group (p<0.02).

LEV was evaluated in a two-week placebo-controlled trial in children and adolescents with newly diagnosed absence seizures. The patients were randomized and received either LEV of up to 30 mg/kg/day (38 patients) or placebo (21 patients). Ninety-two percent of randomised patients suffered from CAE and 8% from juvenile absence epilepsy. After a follow-up of two weeks, nine of the patients treated with LEV (23.7%) and one with placebo (4.8%) were responders (p=0.08). During long-term open-label follow-up, 17 patients were seizure-free with LEV treatment after one year follow-up whereas 34 became seizure-free with another AED (27 children with VPA, six children with ESM and one child with a combination of both).

Overall, the informative value of these open-label studies and short-term double-blind RCTs remained limited. Indeed, their main conclusions were that VPA, ESM and LTG were efficacious in CAE whereas GBP and LEV did not prove more efficacious than placebo. However, whether one of the first three should be preferred as first-line therapy remained an open question because none of the studies was powered enough to formally investigate the relative efficacy of one drug (VPA, ESM or LTG) over the others. Indeed, a meta-analysis of studies comparing ESM and VPA remained inconclusive. Similarly, the treatment guidelines edited by the International League against Epilepsy in 2006 concluded that "VPA, ESM and lamotrigine (LTG) may be considered as candidates for initial monotherapy in CAE," without hierarchy between these three drugs. Importantly, beyond the issue of anti-epileptic efficacy, these studies also poorly addressed the effectiveness of AEDs, which combine both long-term efficacy and tolerability. Indeed, safety issues and specifically cognitive outcomes, were not adequately addressed.

In this context, the National Institutes of Health-funded study published in the New England Journal of Medicine in 2010 by Glauser and colleagues is momentous (see Table 3). Indeed, this large multicenter double-blind RCT, which compared ESM, VPA and LTG in children with newly diagnosed CAE, addressed most of the limitations of previous studies:

- it enrolled a large population, homogeneous in age distribution, seizure type and EEG criteria;
- the dose regimen was flexible, adapted to clinical and EEG responses; and
difficulties (defined as a CPT index >0.60) occurred at baseline with a improved tolerability without comprising efficacy. Moreover, attentional question arises as to whether or not a lower ceiling dose might have the highest recommended dose of VPA is 30 mg/kg/day. Therefore, the titrated up to 60 mg/kg/day whereas in several European countries, 3.04 [95% CI 1.69–5.49], p<0.001). However, in this study, VPA was [95% 1.12–3.41], p=0.03) and with 24% in the LTG group (odds ratio, 1.95 49% of patients on VPA had attentional difficulties, defined as a CPT index >0.60, in comparison with 33% in the ESM group (odds ratio, 1.95 demonstrated greater incidence of neuropsychologic impairment. Thus, VPA did not differ for the primary outcome, the children on VPA randomization and at the end of the treatment period. Although ESM and was significantly lower with a freedom-from-failure rate at 29%. The freedom-from-failure rate was similar in ESM and VPA groups (53 and 58%, respectively). By contrast, LTG effectiveness was observed. The children were considered free from seizures only if no spike-wave burst lasting three or more seconds was detected on the EEG. The highest allowable daily doses were 60 mg/kg for ESM, 60 mg/kg for VPA and 12 mg/kg for LTG. Overall, 209 children (47%) achieved the primary outcome at week 16 or week 20. Treatment failures were related to lack of seizure control in 109 patients (24%) and intolerable side effects in 97 (22%). The freedom-from-failure rate was similar in ESM and VPA children with CAE will progress to juvenile myoclonic epilepsy and/or suffer generalized tonic-clonic seizures at adolescence.5 ESM has been shown to be inefficacious to suppress generalised tonic-clonic seizures. 21 ESM and VPA are the most effective AEDs in this clinical setting; however, their efficacy in CAE remains uncertain. A recent meta-analysis demonstrated a higher frequency in the VPA cohort (42%) than in the ESM (34%) or LTG (30%) cohorts. In addition, although the impact of VPA on the CPT remained statistically significant after adjusting for baseline differences, its effect size proved to be limited (an increase in the rate of attentional dysfunction from 42 to 49%) and of uncertain clinical significance. A clinically relevant primary endpoint was used, defined by the proportion of patients who remained on treatment and were free from both clinical and EEG seizures at the final assessment. Four-hundred and fifty-three children were randomized with a median age of seven years five months: 156 were assigned to ESM, 149 to LTG and 148 to VPA. Dosage was increased every one to two weeks over a 16-week period until the patients were seizure-free or demonstrated treatment side effects. At each study visit, efficacy evaluation used a standardised protocol: if the parents did not report any clinical seizure, up to two five-minute trials of bedside hyperventilation were performed, eventually completed by a one-hour video-EEG monitoring if no seizure was observed. The children were considered free from seizures only if no spike-wave burst lasting three or more seconds was detected on the EEG. The highest allowable daily doses were 60 mg/kg for ESM, 60 mg/kg for VPA and 12 mg/kg for LTG. Overall, 209 children (47%) achieved the primary outcome at week 16 or week 20. Treatment failures were related to lack of seizure control in 109 patients (24%) and intolerable side effects in 97 (22%). 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side effects. Specifically, long-term cognitive and educational outcomes are required. Similarly, several psychiatric comorbid disorders have been reported in CAE. In this context, potential positive or negative impacts of AEDs on psychological status might be important to consider for treatment selection and should be monitored during follow-up. In addition, whether some major chronic effects of VPA, such as weight gain, might emerge as troublesome during long-term follow-up, remains to be investigated. Similarly, for the small percentage of females who will need to continue treatment during adulthood and adulthood to ensure seizure freedom, optimisation of therapy should also take into consideration the available information about the comparative effects of individual drugs on fetal and post-natal development.

In most studies, the responder rates varied between 40 and 60%, highlighting the fact that a significant proportion of patients will require second-line monotherapy and eventually polytherapy. Evidence-based data about the management of refractory CAE are lacking. According to the similar efficacy of ESM and VPA in newly diagnosed CAE, switching from one to the other in case of treatment failure seems to be the most reasonable choice. When patients fail to respond to both ESM and VPA, the probability of achieving seizure freedom with LTG monotherapy is likely to be low. In this context, the combination of AEDs might be proposed, with particular interest in the association of VPA/LTG, which showed some evidence of a positive pharmacodynamic interaction.

Despite the paucity of data, LEV and zonisamide have also been proposed in the treatment of refractory absence seizures. A ketogenic diet and vagal nerve stimulation might be discussed as alternative non-pharmacologic therapies.

Whatever the therapeutic choice, one of the main remaining grey areas in the management of CAE is the issue of treatment duration. About 12 to 19% of children with CAE suffer from seizure recurrence after the withdrawal of AEDs. As for other epileptic syndromes, a delay of two years seizure freedom is usually retained before starting to taper AEDs. This general recommendation might be modulated by the specific characteristics of the epileptic syndrome, such as the presumptive link between the dynamic of CAE and that of brain development, as well as by the presence of individual risk factors, including absence status before or during AED treatment, development of tonic-clonic or myoclonic seizures after onset of treatment and abnormal background on initial EEG. However, we still lack precise and robust data to guide us on the optimal treatment duration in patients with CAE.

Conclusion

Despite the major impact of the recent study reported by Glauser and colleagues, there is still a gap between the prevalence of CAE in pediatric epilepsies and the paucity of available data on its therapeutic management. Beyond the recommendation of preferring ESM as a first-line therapy in newly diagnosed CAE, most of the other issues still require further investigation.